

**UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS**

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK VARIABLE  
LIFE INSURANCE COMPANY, and  
MANULIFE INSURANCE COMPANY (f/k/a  
INVESTORS PARTNER INSURANCE  
COMPANY),

Plaintiffs,

vs.

ABBOTT LABORATORIES,

Defendant.

Civil Action No. 05-11150-DPW  
Hon. Judge Douglas P. Woodlock

**AFFIDAVIT OF JEFFREY MARC LEIDEN, MD., Ph.D.**

1. My name is Jeffrey Marc Leiden. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Educational and Professional Background

2. I am currently employed as a Managing Director at Clarus Ventures LLC, headquartered in Cambridge, Massachusetts. Clarus Ventures is a life sciences venture capital firm.

3. From July 2000 until March 2006, I was employed by Abbott Laboratories ("Abbott"), initially as Senior Vice President and Chief Scientific Officer, and then as President and COO of the Abbott Pharmaceutical Products Group. I also served on Abbott's Board of Directors during this time period.

4. I received my undergraduate degree from the University of Chicago in 1975. I received a Ph.D. in Virology and Molecular Genetics from the University of Chicago in 1979, and an M.D. degree from the same school in 1981. From 1987-2000, I held several academic appointments including Chief of Cardiology and Director of the Cardiovascular Research Institute at the University of Chicago, the Elkan R. Blout Professor of Biological Sciences at the Harvard School of Public Health, and Professor of Medicine at Harvard Medical School. During my academic career, I was involved in starting several biotechnology companies including Vical, Inc. and Cardiogene Therapeutics, Inc. I am an elected member of both the American Academy of Arts and Sciences and the Institute of Medicine of the National Academy of Sciences.

5. I joined Abbott in July 2000 as a Senior Vice President and Chief Scientific Officer. At that time, Abbott was organized into five divisions: Pharmaceutical Products, Hospital Products, Diagnostics, Ross Nutritional and Abbott International. I was responsible for overseeing and providing advice on scientific programs within all of these divisions. In September 2000, I became Executive Vice President of the Pharmaceutical Products Group ("PPG"). In 2001, I became President and COO of the Abbott Pharmaceutical Products Group. In addition to my previous duties, I became the senior Abbott executive responsible for the businesses of that group, which included research, development and manufacturing of all of Abbott's pharmaceutical products. I held that position until I left Abbott in March 2006. I reported directly to Miles White, Abbott's Chief Executive Officer and Chairman of the Board. Among my responsibilities was to oversee Abbott's pharmaceutical research and development programs at all stages of development. It was also my responsibility to

serve as the chair of a senior management group, whose members included heads of project teams, commercial R&D and manufacturing leaders and regulatory personnel, who together made decisions about prioritizing Abbott's R&D investments, assigning budgets to particular developmental drugs and ultimately determining whether to continue or terminate drugs in various stages of development. Sometime in 2001, that group became formally known as the Pharmaceutical Executive Committee ("PEC").

6. Research and development is a critical component of the pharmaceutical industry. Pharmaceutical companies are R&D intensive, and they spend more as a percentage of net sales on R&D in bringing new products to market than most other industries. When I joined Abbott in 2000, it was making significant investments in R&D and in bringing new drugs and other products to market. For example, in 2001, Abbott's pharmaceutical R&D had approximately 35 drugs in various stages of development but not yet approved by the FDA. The amount expended by Abbott on R&D for all of its products in that year approximated \$1,491,800,000 representing 10.7% of its sales.

7. Only a small percentage of the chemical compounds that are synthesized as pharmaceutical products ever reach clinical trials (1 per 1000 to 1 per 10,000), and only a fraction of those are ultimately approved by the FDA (less than 1 per 10). Abbott, like other pharmaceutical companies, must spend significant amounts of money on research and development for drugs that are never brought to market. These expenditures include the cost of clinical trials to assess the safety and efficacy of the drug, compensation for scientist and researchers for doing preliminary research, and the cost of FDA submissions. There are many reasons why developmental drugs are never brought to market, including inability to demonstrate sufficient efficacy and the presence of side

effects which can prevent approval or lead to insufficient commercial advantage, or the presence of other compounds in the portfolio which compete for investment dollars and demonstrate greater potential.

8. Because of the enormous costs and risks of pharmaceutical R&D, Abbott has on a number of occasions sought out the participation of outside companies in various forms of collaboration with respect to developmental drugs. The amount that Abbott could invest at any given time in the research and development of new compounds was not unlimited and such transactions potentially allowed Abbott to try to develop more of the compounds in its pipeline than would otherwise be the case. The Research Funding Agreement (“RFA”) between John Hancock Variable Life Insurance Company (“Hancock”) and Abbott, executed in March 2001, was one such transaction.

9. I did not personally negotiate the RFA with Hancock but I signed the agreement on behalf of Abbott. It was my understanding that the purpose of the RFA was to obtain approximately \$200 million from Hancock which would be used towards funding a basket of Abbott developmental compounds in return for royalties on sales that Abbott might achieve on any drugs that were actually approved. I believed that the RFA was in Abbott’s interest and in the best interest of patients because it potentially might allow Abbott to develop more developmental compounds than it could otherwise to afford to do. I was not involved in the selection of the particular developmental compounds that we included in the RFA with Hancock. However, I was aware that they were in different stages of development with accordingly different risk profiles.

10. The PEC generally met twice per year to review all of Abbott’s R&D programs. During those meetings, program leaders for each of the compounds in various



stages of development would present the status of the programs to the entire group as part of a portfolio review. The group would then meet in executive session to make determinations with respect to the R&D plan and the R&D budget, including whether any events had occurred that warranted discontinuation of development (for example, unfavorable clinical trial results or changes in the competitive or regulatory environments).

11. At the end of 2000, Abbott acquired the Knoll Pharmaceutical Division of BASF Corporation ("BASF"). As part of that acquisition, Abbott acquired a new set of R&D compounds or projects as well as increased R&D funding that had been allocated by BASF to those projects. In order to put the two sets of development projects together, examine the total budget, and prioritize the combined portfolio, we held a special Portfolio Review Meeting from March 7-9, 2001 at the Hyatt Deerfield, in Deerfield, Illinois. Similar to the bi-annual portfolio review meetings, each program leader for every compound in development at both companies made a presentation to the Pharmaceutical Products Group leadership regarding the status and prospects of the compounds for which they were responsible. Attached hereto as D's Exhibit 621 is a true and correct copy is an agenda for the portfolio review meeting showing the compounds which were reviewed at the meeting. They included drugs in the categories of anti-infectives, urology, asthma, oncology, cardiology, thrombosis, neuroscience, and gastroenterology. According to the agenda, approximately thirty-five compounds in development were discussed at the meeting, as well as ten drugs already being marketed that were the subject of additional R&D. The presentations took place over three full

days. Each of the nine compounds in the basket that were included in the RFA with Hancock was presented just like every other drug in the Abbott/Knoll portfolio.

**ABT-518**

12. During this portfolio review meeting, Dr. Perry Nisen, who was the Vice-President of Oncology Development in 2001 (the unit of the PPG responsible for development of potential cancer drugs), gave a presentation regarding a compound called ABT-518. ABT-518 is a Matrix Metalloproteinase Inhibitor (“MMPI”), a new class of compound that we hoped would be efficacious in the treatment of cancer. It was one of the nine compounds included in the Hancock investment.

13. According to the agenda, the presentation lasted for fifteen minutes and the discussion for the group was to take place for five minutes thereafter. To the best of my recollection, these time periods generally corresponded to what actually transpired. Attached hereto as D’s Exhibit 782 is a true and correct copy of the slide presentation which I believe Dr. Nisen presented at the portfolio review. To the best of my recollection, this was the first substantive presentation I had attended with respect to this compound since I joined Abbott.

14. A number of other companies were seeking to develop MMPIs as well, and some were in advanced clinical development. By contrast, ABT-518 was an early stage compound that was just scheduled to enter Phase I clinical trials (first in-human small scale study). I learned during the presentation that some competitors’ MMPI compounds had experienced difficulties in clinical trials, such as side effects involving musculoskeletal pain and stiffness in the joints (“joint toxicity”) and had not yet demonstrated efficacy. Dr. Nisen expressed the belief that the Abbott compound would

be able to avoid these problems and demonstrate efficacy in some indications based upon the promising pre-clinical work that had been done to separate efficacy from toxicity. The preclinical data showed that ABT-518, compared to the competitors' compounds, was highly selective for the inhibition of gelatinase A and B (which play a role in tumor progression), very potent, and was not expected to produce joint effects. However, the competitive data available to date was very limited, because the companies had not published the clinical trial data from their most recent trials, including all of the information regarding clinical study protocols, the numbers of patients, primary and secondary efficacy endpoints, and other detailed scientific data that is generally necessary to evaluate clinical trial results. We were particularly interested in clinical data regarding Pfizer's recent studies because its MMPI compound, Prinomastat, was being tested in advanced stage (Phase III) trials and, like ABT-518, was more gelatinase selective than the other MMPI compounds (although it was not as selective as ABT-518). Also, Pfizer had not presented at the 2000 American Society of Clinical Oncologists ("ASCO") conference, therefore, available clinical data regarding this compound was particularly outdated.

15. Following Dr. Nisen's presentation, the senior management group had a brief discussion about ABT-518. The principal question regarding this compound was whether it could be distinguished from competitive MMPI compounds or whether the negative results that had been available to date indicated the possibility of class wide effects that would apply to ABT-518 as well. We did not believe that we could make this determination in the absence of clinical data concerning recent trials of the competitive compounds. The annual meeting of the ASCO was scheduled for mid-May. This is the

most important conference in the oncological field, and we knew that detailed information concerning competitive MMPI compounds including peer-reviewed reports of the clinical data was going to become available at that conference. Accordingly, we believed that we should put a temporary hold on the Phase I clinical trial, which was just beginning, to await this information. If the clinical trial data at the ASCO conference was sufficient to convince us that there was a good likelihood of distinguishing ABT-518 from the competitive compounds or that the problems that had been generally reported were likely not class wide, we could then begin the clinical trial with minimal delay. If, on the other hand, the ASCO results revealed that, given the specific clinical data regarding other compounds in the class, the efficacy or toxicity problems would likely also exist with ABT-518, we would not have expended funds which could have been used for other R&D compounds. The committee therefore instructed Dr. Nisen to put a hold on further ABT-518 activities until after the ASCO conference.

16. Within days of the March 7-9, 2001 Portfolio Review Meeting, Dr. John Leonard, then Abbott's Vice President for Global Pharmaceutical Development (who reported directly to me) and Dr. Nisen met with me to express their disagreement with that decision and seek a reversal of it. They reiterated their belief that the pre-clinical work on ABT-518 showed ABT-518 had the potential to distinguish itself from the competitive compounds. They pointed out that, because Abbott was behind other companies in MMPI development, even the few months we would lose by putting a hold on the Phase I trial could place Abbott at a competitive disadvantage should the clinical data at ASCO validate continued development of ABT-518. They also explained that the costs to continue the Phase I clinical trial were not high, and if that data subsequently

suggested that ABT-518 should not be developed, we could stop the program at that time. I found these arguments persuasive, and told Dr. Leonard and Dr. Nisen that the hold should be lifted. The clinical trial was resumed shortly thereafter and, to my knowledge, the brief temporary hold that had been placed on the clinical trial until the ASCO results could be obtained and analyzed had no impact on the developmental schedule for ABT-518.

17. I understand Dr. Leonard believes he may have mentioned the upcoming Hancock Agreement to me during this meeting to remind me that we had additional funds to invest in ABT-518 which would improve the risk profile of the compound. I do not have a specific recollection of discussing the Hancock Agreement in this conversation. In any event, the Agreement with Hancock played no role whatsoever in my decision to lift the hold. That decision was based solely on the arguments put forth by Drs. Leonard and Nisen, in which they indicated that the costs of delaying the trial until after ASCO outweighed the benefits. Before and after the decision, with respect to the temporary hold, it was without question our intent to make no decision about the future of ABT-518 until we obtained the results from the ASCO conference and were able to analyze them and determine their applicability to ABT-518. As discussed below, that is exactly what we did.

18. I understand that Hancock claims a document entitled "Initial Portfolio Prioritization" shows that Abbott had decided to terminate ABT-518 at the March 7-9 portfolio review. I have examined this document, which has been marked as Plaintiff's Exhibit PT in this case. This is not a document that I recognize as being prepared by anyone within Abbott in the ordinary course of business or otherwise at my direction. I

have no recollection of ever seeing this document, or any other document in a similar format, until my deposition in this case. I understand that the document was sent to me electronically by an employee of McKinsey and Company, Inc. ("McKinsey") named Jessica Hopfeld. McKinsey was retained by Abbott in connection with the Knoll acquisition and generally had a number of people present at meetings in which we discussed integration of the portfolio and other strategic questions related to the transaction. I do not recall instructing McKinsey to prepare this or any other summary of specific compound decisions.

19. To the extent that the entry under ABT-518 "hold - wait for May results from Pfizer - (will save \$1 million) and reevaluate" refers to the hold placed on the compound which was then lifted shortly thereafter, and that the "May results" refer to the ASCO conference data, it is consistent with my memory of the decision made at the portfolio review meeting. I do not know what is meant by the phase Hold/T (terminate), which appears in one version of the document. There was certainly no decision, at that meeting that ABT-518 would be terminated without a thorough review and evaluation of the ASCO data.

20. The ASCO conference was held on May 12-15, 2001. On May 28, 2001, I subsequently attended a presentation by Dr. Nisen and other members of the ABT-518 team regarding the data obtained at the conference. While, as stated above, some limited, general information regarding recent trials of competitive compounds had been available in press releases and news reports before ASCO, we obtained for the first time at the ASCO conference the detailed clinical and scientific data that was necessary to make a decision about whether the development of ABT-518 should proceed. Indeed, it is my

understanding that, under the rules of the ASCO conference, information which had previously been made available publicly was not eligible to be published at the conference. By definition, therefore, the data that we obtained and relied upon was not known to Abbott until the conference was held.

21. Attached hereto as D's Exhibit 586 is a true and correct copy of the presentation prepared by the project team summarizing the data obtained at the ASCO conference, which was presented to me on May 28, 2001. In the oral report that accompanied this presentation, Dr. Nisen also provided additional details regarding the clinical data. Although I do not recall all the details provided by Dr. Nisen regarding the ASCO clinical data, I recall generally that he reported information such as the numbers of patients and the protocols of the studies. As reflected in the presentation, Dr. Nisen reported that "negative findings" regarding Prinomastat, Marimastat, and Bay 12-9566 were released at the conference. He reported that the clinical data from Pfizer's Phase III trial of Prinomastat in patients with non-small cell lung cancer showed "[n]o survival benefit" and that data from a Phase III trial in patients with hormone refractory prostate cancer showed "[n]o effects on PSA [i.e., a prostate specific antigen protein that is measured to track cancer progression.], progression free survival, [or] overall survival." As reflected in the presentation, Dr. Nisen reported that Pfizer released the results of a Phase I/II trial of Prinomastat as a "single agent" (*i.e.*, not in combination with other therapies) in 44 patients with refractory metastatic breast cancer. In his oral report, Dr. Nisen noted that the efficacy data from that trial also was negative. In addition, Dr. Nisen reported that the data from all three trials showed grade 2 joint toxicity at all dose levels (5, 10, and 15 mg twice-a-day). Dr. Nisen also reported negative data from British

Biotech's trials of Marimastat. For example, as reflected in the presentation, he reported that the data from British Biotech's small cell lung cancer study showed "no benefit on progression free survival or overall survival." In addition, Dr. Nisen reported that the clinical data from Bayer's trial of Bay-12-9566 in patients with ovarian cancer showed "[n]o benefit on survival." Dr. Nisen concluded by recommending that Abbott complete the ongoing Phase I trial of ABT-518 prior to making a final decision on how to proceed.

22. Based upon the data we obtained at the ASCO conference, the PEC concluded, shortly after the May 28, 2001 presentation, that Abbott should not proceed with further development of ABT-518. The clinical data showing a lack of efficacy of Prinomastat and other compounds in advanced trials involving a range of cancers, as well as the joint toxicity experienced by the competitors, led to our decision to terminate the program. We had hoped that ABT-518, because of its greater selectivity, could avoid the side effects of the competitive compounds and be administered in larger doses to achieve greater efficacy. However, we concluded, based on the ASCO data, that there was a greater likelihood of class-wide efficacy and joint toxicity problems with the MMPI compounds than we anticipated based on the clinical data from animal testing of ABT-518. We concluded that, based upon the clinical data that we had obtained from ASCO, it was very unlikely that ABT-518, despite its greater potency and selectivity, would have the kind of efficacy and safety needed to justify further the investment in the project.

23. I understand that Hancock is contending that Abbott reviewed its supposed March decision to discontinue development of ABT-518 at an early May 2001 strategy review, before the ASCO conference was even held. While I do not recall the specifics of this review, I can unequivocally and without reservation state that Hancock's



contention regarding when the decision was made is not true. Strategy retreat meetings of this kind were held periodically and were high level reviews of our therapeutic areas. The presentations generally focused on market dynamics, general scientific opportunities, and the competitive landscape. We did not make project decisions at these forums because the presentations and discussions were focused on overviews of the therapeutic areas and not on specific project reviews. I have reviewed the oncology presentation that was given during this strategy retreat and it is consistent with my recollection that no decision was made at this meeting. Furthermore, if this decision had been made at the May strategy review, there would have been no reason for senior management to analyze the results of that conference on May 28, 2001 as we did. It was always our intention to make a decision on ABT-518 based upon the scientific data that we knew would become available at the ASCO conference and that is exactly what we did.

#### **ABT-594**

24. ABT-594 was another compound in development at Abbott in 2001 which was included in the basket of drugs in which Hancock invested. ABT-594 was in the class of pharmaceutical compounds known as Neuronal Nicotinic Receptors (“NNRs”). We believed that ABT-594 was a promising novel pain medication which had the potential to be the first compound in its class to be approved. However, we were also aware that in the Phase I clinical trial results, some patients who had been given a relatively low dose of the drug had experienced adverse events, including nausea, headache, dizziness, insomnia and vomiting.

25. The compound moved into a Phase IIb clinical study in April 2000. The final results of that study were expected to become available in mid-2001. One of the

major issues to be determined by that clinical trial was at what dose the compound was most efficacious, and whether the side effects at that dose could be minimized so as to justify further investment in its development. The relationship between a proper dose for efficacy and an acceptable toxicity or side effect profile is known as a therapeutic index.

26. I was familiar with the general design of the Phase IIb clinical trial for ABT-594. The trial was what is known as “dose ranging” because it was designed with four different dosages: placebo (containing no drug at all), 150 mcg, 225 mcg, and 300 mcg. One of the purposes of designing the study in this manner was to include dose levels that were higher than that believed necessary to achieve efficacy so that the side effect profile for the drug could be developed. Accordingly, we expected that at the higher doses there would be drop outs from the study that would occur because of side effects. However, during the course of the clinical trial, it would be impossible to know at what dose any drop outs were occurring. This is because the clinical trial was “double blinded.” A double blinded clinical trial is one in which patients receiving the drug, the investigators administering the drug, and the sponsor of the clinical trial (i.e. Abbott), do not know which dose each patient is receiving. Information correlating side effects, efficacy and other clinical results with the dose given each patient is not released or “unblinded” until after the entire trial has been completed.

27. I was aware of and agreed with a decision by the PEC to enroll less than the original target number of patients in the Phase IIb clinical trial. It is not uncommon for clinical trials to experience some slowness in reaching target enrollment on schedule, nor is it unusual to experience patient drop outs in a study for a variety of reasons, including adverse events. It is typical at Abbott that, as enrollment in a clinical trial was

coming to an end, the question of whether the study could be completed on a timely basis with fewer subjects was discussed. This is because the loss of time in obtaining clinical results can cause a delay in ultimate approval and development of the product, which in turn can lead to a loss of market opportunity and revenue. In the case of this clinical trial, the PEC was informed that an analysis had been performed by Abbott statisticians to determine whether reducing the number of enrollees from 320 to 269 would have any effect on the statistical reliability of the results and that they concluded it would not. Accordingly, Dr. Leonard informed the PEC that we could complete the study with the smaller number of patients and save a significant amount of time and money. The PEC approved this change in enrollment.

28. I have no recollection of any presentation to me or to the PEC in which the issues of drop out rates or reduction in enrollment from the clinical trial was discussed as a reason for substantive concern with respect to the ultimate success of ABT-594. I attended a detailed presentation on ABT-594 by Chris Silber, Venture Head for The Analgesia Venture, and other members of the ABT-594 development team, including Dr. Bruce McCarthy, on February 2, 2001. Attached hereto as D's Exhibit 748 is a true and correct copy of the slides that were presented at that time. There was no mention in the presentation of any concern that drop outs or the reduced enrollment might affect the ultimate likelihood of success of the clinical trial nor do I remember any such discussion. To the contrary, the project team reported that the reduction in enrollment in the study would not affect its statistical validity:

## M99-114 Status

- Enrollment
  - Ended 1/5/01 at 269 subjects
  - Pre-specified power not reached
  - Width of confidence intervals not meaningfully different between 269 and 320 enrolled
- Database release – 5/01
- Go/No Go – 6/01

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29. There was also a presentation of ABT-594 at the March 7-9, 2001 Portfolio Review Meeting, which previously I referred to in my testimony above. Attached hereto as D's Exhibit 620 is a true and correct copy of the presentation slides for this meeting. Again, there was no information presented at that meeting regarding interim data from the clinical trial nor any expression of concern that the prospects for ABT-594 would be affected by the drop out rate or reduction of enrollment in the clinical trial. Nor was there any presentation or analysis of interim or blinded results from the

clinical study. Moreover, I believe that any concern based upon such data would have been completely unwarranted. The drop out rate in the ABT-594 clinical trial was not unusual, particularly in a pain trial, and, in a double blinded study like this one, no conclusions could be drawn from it. This is because, as I explained above, it was expected that at the higher doses there would be drop outs from side effects, and indeed, those doses had been selected specifically to define an adverse event profile. Without knowing what doses were administered to the patients who had dropped out, it was entirely possible and likely that the adverse events were suffered by patients who were administered higher doses, which might be higher than needed to achieve efficacy. In addition, drop outs often occur for other reasons, including the fact that patients receiving the placebo who suffered from pain were not permitted under the protocol to be on any other pain medication. For those reasons, it is well known among those experienced with clinical trials that no conclusions can be drawn from dose-ranging blinded clinical studies of this type until the results have been unblinded. This is particularly true in pain trials.

30. I do not recall any discussion whatsoever, during that meeting or any other meeting which I attended prior to the unblinding of the Phase IIb clinical trial results, that ABT-594 would probably be terminated. Rather, consistent with every discussion I am familiar with regarding ABT-594, the consensus was that a Go/No Go decision on this compound would be made based upon the unblinded results of the Phase IIb clinical trial, which were expected to be available in one to two months.

31. I have reviewed the document generated by McKinsey which I understand Hancock claims contains an entry reflecting discussions held at the March 7-9, 2001 Portfolio Review Meeting about ABT-594. As I previously have stated, I have no

recollection of seeing this document at the time, although apparently it was e-mailed to me by someone at McKinsey. I can say that, to the extent this document is claimed by Hancock to reflect a decision by senior management that ABT-594 would probably be terminated before the results of the Phase IIb clinical trial were unblinded, it is completely inaccurate and does not describe anything that I recall from that meeting. I have not seen any documents generated by Abbott, as opposed to McKinsey, that reflect any discussion, much less a decision, that ABT-594 would probably be terminated, prior to the unblinding of the clinical trial results.

32. The blind on the ABT-594 clinical trial was broken and results available at the end of April 2001. Attached hereto as D's Exhibit DN is a true and correct copy of the April 27, 2001 Monthly Highlights Memo that was sent to me by Dr. Leonard. I attended several meetings of the PEC after the results had been analyzed to discuss the future of ABT-594. For example, on August 21, 2001, the PEC conducted a review of ABT-594 in which the unblinded clinical results were discussed. Attached hereto as D's Exhibit 784 is a true and correct copy of the presentation made by the ABT-594 project team to PEC at that meeting. The project team, reporting on the unblinded clinical results, stated that: "ABT has a narrow therapeutic window and efficacious doses are poorly tolerated as dosed currently." *Id.* at ABBT0184374. In other words, we had learned from the unblinded clinical results that the doses which were needed to achieve significant efficacy also led to an unacceptable level of side effects. The team also reported that the Decision Analysis Strategic Group within Abbott had analyzed ABT-594 to determine its commercial value if modifications to improve tolerability were made and had concluded that "that the expected value for these modifications is small, although

positive. *Id.* In other words, it was being projected that the compound, as modified, would still generate some positive revenue, but not a significant amount.

33. The PEC further met to consider ABT-594 on October 8, 2001. There was some discussion of whether another dosing clinical trial should be held to determine whether modifications to dosing methods to improve the tolerability of ABT-594 should be attempted. However, after careful review, the decision was made to terminate internal development of the compound. We concluded, based upon all the available information, that although ABT-594 had efficacy at certain dosage levels, the side effect profile at those levels would limit the commercial upside and make it an unattractive investment for Abbott.

#### **ABT-773**

34. ABT-773, a compound that was also one of the nine compounds in which Hancock invested, was an antibiotic known as a ketolide that Abbott was developing for four indications: acute bacterial exacerbation of chronic bronchitis, pharyngitis, community-acquired pneumonia ("CAP"), and acute bacterial or maxillary sinusitis.

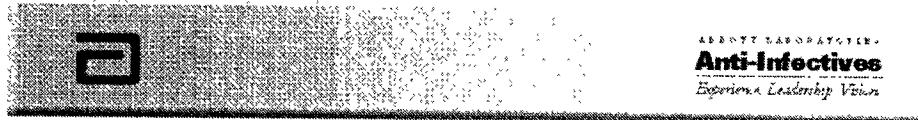
35. In December 2000, I attended a presentation in which the ABT-773 project team provided an overview of the status of the project to me. Attached hereto as D's Exhibit 787 is a true and correct copy of the December 2000 presentation slides. This was the first formal presentation I recall receiving on that compound since I joined Abbott. At that time, ABT-773 was one of the top projects under development at Abbott given the value it was expected to have to the company and the fact that it was already at a late stage of development.

36. Potential regulatory issues with respect to the approval of ABT-773 were discussed at the presentation. Specifically, there was discussion of the potential for abnormal heart beat prolongation (known as “QT” prolongation). The issue involved a generalized FDA concern with respect to all therapeutic drugs submitted for Agency approval, and most specifically with a broad class of anti-infectives known as macrolides, which had been well known for years to have potential QT effects at high doses. (Despite these issues, Abbott’s Biaxin® antibiotic, a macrolide, has been a hugely successful drug). The FDA was asking whether “ketolides behave like macrolides.” *Id.* at ABBT205225. My understanding from that presentation and other information I obtained from the project team, however, is that there was no data whatsoever that suggested there was any actual issue with QT prolongation with respect to ABT-773. To the contrary, all of the data we had developed in the Phase II clinical trials showed the lack of any significant QT effect. The only dose effect that had been noted was in small samples in the Phase I trials at doses of 800 mg, many times the dose that was expected to be prescribed to patients. A slide from the December 2000 presentation summarizing the data on this issue is below.



**Summary of ECG**

- A possible dose effect in Phase I at total daily dose  $\geq 800\text{mg}$ .
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole.
- No concentration response in Phase I studies ( $\leq 300\text{mg}$ ).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies.
- Will continue to monitor QT in Phase III programs.



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As reflected in this slide, we were told by the project team that: “no consistent QT effect [had been] observed at clinical doses studied in Phase IIB studies.”

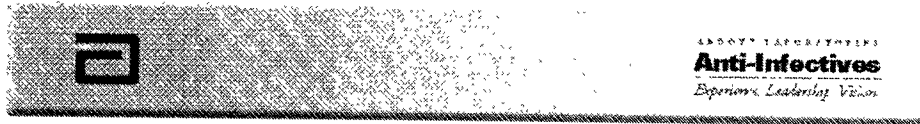
37. The issue of potential liver toxicity was also discussed at the December ABT-773 meeting. We were informed that in 2000 there had been a single small Phase I study in a Japanese population as part of the development program, which included Japanese patients living in Hawaii. In that study, there were a few patients who demonstrated elevated liver function toxicity (“LFT”) levels. However, the results were completely at odds with what we had observed in the other clinical trials for ABT-773. Those clinical trials, which had included several hundred patients, did not demonstrate any liver issues, so the results of the study appeared to be an anomaly. Like the QT prolongation issues, FDA was looking at liver toxicity as a potential issue for all antibiotics and had not cited any particular data or other basis for concern with respect to ketolides generally or ABT-773 in particular. At the December 2000 presentation, the project team reported to the management group that there was no “evidence of LFT issue

in western subjects” and “no consistent evidence of dose response.” It was agreed that the Japanese bridging study results should be confirmed. Below is a copy of that presentation slide.

***LFT Summary***

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- No evidence of LFT issue in Western subjects.
- No consistent evidence of dose response.
- Japanese bridging study results should be confirmed.
- Will continue to monitor LFT in Phase III programs.



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38. I attended a PEC presentation regarding ABT-773 on March 19, 2001. This was only a few days after the RFA between Hancock and Abbott was signed. Attached hereto as D's Exhibit 631 is a true and correct copy of the presentation slides. QT prolongation was again discussed, and it was affirmed that there was no data indicating that ABT-773 had any QT issues at normal doses. During the presentation it was reported that “no clinically relevant QT effect in Phase II studies 150-600 mg. daily” was found in a large study of 412 patients:

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# QT Prolongation

- Purkinje fiber repolarization
  - APD increase at 5 mcg/mL (10x clinical Cmax) in the absence of plasma proteins, but not in their presence
  - Moxi > Clari > Ery ~ ABT-773 > Levo (without plasma)
- Dogs
  - no significant effect on QTc up to 9 mcg/mL
  - 11% increase (40 msc) at 22 mcg/mL
  - Telemetry-instrumented dog study requested by FDA will be completed by May 1, 2001
- Humans
  - Possible dose effect in Phase I at daily dose > 800 mg
  - No significant QT effect in ketoconazole interaction study
  - No clinically relevant QT effect in Phase II studies 150 – 600 mg daily (n=412)

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39. With respect to liver toxicity issues, we had repeated the study with Japanese subjects to determine whether slight liver elevations were caused by the drug or by diet of the Japanese population. The project team reported at the March 19 update that the results confirmed that there was no evidence whatsoever of liver toxicity issues.

Highly Confidential

# Hepatotoxicity

- Toxicology studies
  - NTEL for LFT abnormalities in rat = 3-8 x clinical AUC
  - NTEL for LFT abnormalities in monkey = 2-4 x clinical AUC
- Clinical experience
  - No evidence of LFT issue in Western subjects (<1% asx LFT elevation in >1000 pts in phase II-III studies)
  - Japanese in bridging study showed increased LFTs.
    - 7 of 42 (17%) Japanese subjects had >3x ULN
    - No evidence of dose response
    - Repeat study in Japan showed no evidence of LFT increases in Japanese (n=60) or Caucasians (n=8).

ABB120481.UR

40. In sum, as of March 2001, based on all of the data available to Abbott, there was no basis to believe ABT-773 had serious safety issues that would pose an obstacle to FDA approval of the compound.

41. I was generally aware that it was one of the goals of the ABT-773 program to achieve once per day dosing (QD) for all indications for which approval was planned to be sought. However, I also understood that once per day dosing was much more important for the two less severe and more commercially significant indications, chronic

bronchitis and pharyngitis, and that dosing might be twice a day (BID) for the more severe indications of pneumonia and sinusitis. By the March 14, 2001 update, we had sufficient data to select once per day dosing for bronchitis and pharyngitis, but needed further clinical trial results to decide the proper dosing for the other two indications. The updated presentation reported the dosing status at that time. "150 mg QD selected for ABECB and pharyngitis in pivotal Phase III comparative studies. 150mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS." D's Exhibit 631 at ABT120488.UR.

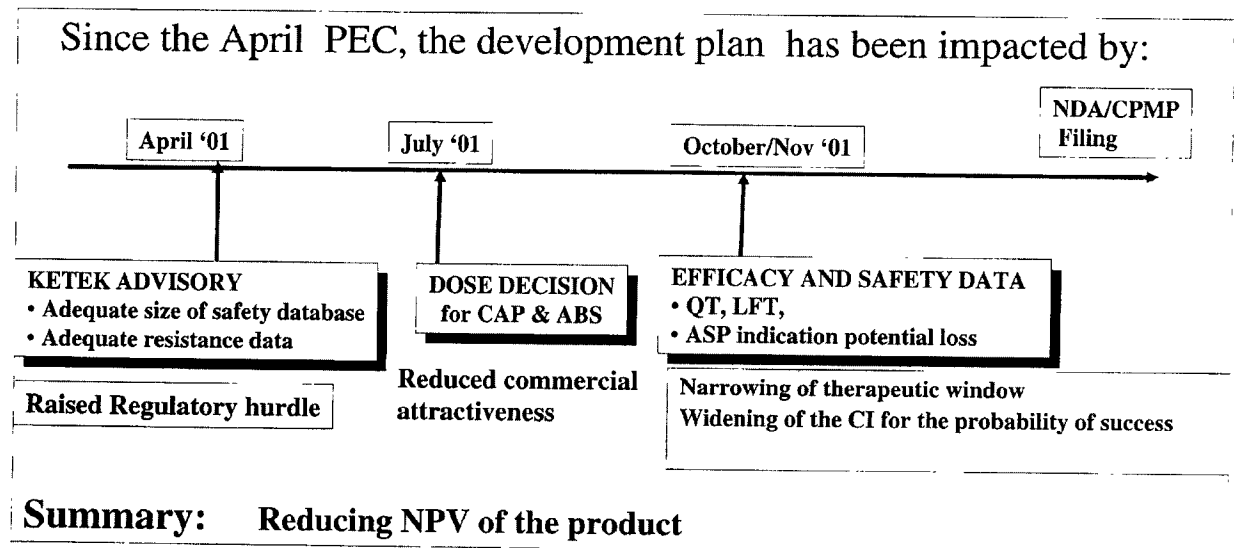
42. The clinical data necessary to make this dosing decision was not going to become available until July 2001, and it was presented to me and Dr. Leonard at that time. Attached hereto as D's Exhibit DO is a true and correct copy of the August 10, 2001 Monthly Highlights memo reflecting that a presentation was made to senior management on this issue. Based upon that data, we decided to pursue twice a day dosing for the more severe indications. The decision was based on the fact that we did not have sufficient information as of July 2001 to determine whether once-a-day dosing would be sufficient for the more severe indications. Rather than wait for additional data and slow down the development of the compound, we decided to proceed with twice-a-day dosing. We believed this decision would have a limited impact on the commercial prospects of this compound for several reasons. First, there are many drugs on the market for those indications that were twice a day or three times a day. Second, these indications are a much smaller part of potential market for ABT-773. Third, we expected that we would be able to launch ABT-773 with once-a-day dosing for the more severe indications one year after its initial launch with twice-a-day dosing. Finally, twice a day

dosing is only a minor factor in markets outside the United States, which were expected to constitute almost half of the sales for these two indications (and is actually preferred in Japan).

43. In December 2001, the Pharmaceutical Executive Committee met to review a number of events that had occurred since April 2001 that had substantial adverse effects on the prospects for ABT-773. Attached hereto as D's Exhibit EC is a true and correct copy of the Agenda and slide presentation for that meeting. As summarized in the presentation, these developments fell within three categories:

Highly Confidential

## ABT 773 Team Summary and Recommendations



ABT120515 UR

2

44. The term "KETEK ADVISORY" on this page refers to an advisory meeting that the FDA held regarding Ketek, a competitive ketolide that was under

development by another pharmaceutical company, Aventis, and was expected to be the first ketolide to be approved for marketing. However, instead of approving the drug, the FDA determined that there was insufficient data to demonstrate that there were no issues with respect to QT prolongation and liver toxicity. The FDA also determined that the data supporting a resistance claim for Ketek was insufficient. Instead, Aventis was going to be required to perform a 20,000 patient study to demonstrate the safety of its drug and substantial additional data to support a resistance claim. The effect of the Ketek advisory was presented to Abbott's Board of Directors, of which I was a member, in a September 7, 2001 Operations Highlights, as causing a one-year delay in the development of the compound. Attached hereto as D's Exhibit 501 is a true and correct copy of the September 7, 2001 Board of Directors Operations Highlights.

45. "DOSE DECISION" refers to our determination, in July 2001, that two of the four indications would be twice daily, at least at the time of launch. However, in November, the Phase III trial results for the pharyngitis indication showed that ABT-773 dosed once daily had insufficient efficacy for approval. These results cast substantial doubt upon the potential for once a day dosing in the remaining indication, bronchitis.

46. The heading "EFFICACY AND SAFETY DATA" refers to new data from the Phase III clinical trial results which we obtained in November, 2001. Some liver and enzyme elevations had been observed in a few subjects in those clinical trials. Although the severity and incidence of these effects were in an acceptable range for antibiotics, there was concern that the findings would require a much larger safety database. Second, because the Phase III pharyngitis trial had shown insufficient efficacy, we stood to lose the biggest single indication that had been projected for ABT-773. Pharyngitis

represented 53% of the potential market for ABT-773, with a net present value of more than \$117 million.

47. In January 2002, Dr. Stan Bukofzer and Dr. Eugene Sun, who were responsible for the ABT-773 project, wrote a Memorandum to Abbott's CEO, Miles White, on behalf of the PEC, recommending that the development of ABT-773 be suspended because of the adverse events that had occurred beginning with the Ketek advisory in April 2001. Attached hereto as D's Exhibit 761 is a true and correct of the January 2002 Memorandum. The Memorandum sets forth in greater detail the reasons for that recommendation. As stated in the letter, the PEC was "extremely disappointed to recommend stopping a key Phase III program in development," one that we had expected to be a top value asset in the portfolio and in which we had already invested hundreds of millions of dollars. However, I believe the PEC's recommendation was the correct one, given the uncertainty, increased regulatory hurdles, and diminished commercial value caused by the adverse developments I have described. The Memorandum also provided a summary of the events since March 2001 that had caused ABT-773 to diverge from its target product profile, including the loss of the pharyngitis indication:

In November, the pivotal U.S. Phase III trial in pharyngitis showed that ABT-773 dosed once daily at the chosen dose had insufficient efficacy for approval. Additionally, these results cast some doubt on the potential for QD dosing for bronchitis.

*Id.* at ABBT0559668. The loss of the pharyngitis indication was "forecasted to erode more than \$117MM in NPV from ABT-773 . . ." *Id.* at ABBT0559670. The Memorandum also noted that the resistance claim we had been seeking for ABT-773 would be "challenging to achieve" based on new information from the April 2001 Ketek advisory:



The resistance claim is based on successful treatment of pneumonia patients who have resistant organisms. The original ABT-773 plan targeted approximately 15 such patients. In 2001, the EMEA and FDA evaluated telithromycin (Ketek), Aventis' first-in-class ketolide. Neither the EMEA nor the FDA considered the Ketek data sufficient to support a resistance claim based on 17 patients with about an 85% eradication rate. It is now anticipated that a resistance claim for ABT-773 will require a larger number of resistant isolates (this requirement will significantly increase the size, complexity and duration of clinical trials) as well as an eradication rate of at least 85%.

*Id.* at ABBT0559669. Finally, the safety database that would be required by the FDA had increased dramatically since the Ketek advisory, causing us to conclude that:

QT prolongation by ABT-773 has not been fully characterized and remains a potential liability. In recent years, broad regulatory attention to this issue has resulted in increasing requirements for in vitro as well as clinical data to assess this risk. To date, data indicates that QT prolongation by ABT-773 is comparable to clarithromycin and Ketek, but FDA has requested additional studies. Should these studies suggest clinically significant risk, regulatory actions could include non-approval, Black Box warning, or contraindication in at-risk populations.

*Id.* at ABBT0559669. The Memorandum also noted the liver enzyme elevations that had been observed in the October 2001 clinical trial and noted that while the "incidence and severity of these findings fall within an acceptable range for antibiotics, future findings may drive the requirement for a larger safety database." *Id.* at ABBT0559670. Our decision ultimately proved to be correct since Ketek, which was ultimately approved by the FDA subject to warning labels and an enormous amount of additional clinical work, has been a remarkably unsuccessful drug for Aventis.

48. Ongoing work for clinical studies and other projects for ABT-773 continued through the spring of 2002. During this time there were several clinical studies that were continuing and we were internally analyzing whether to discontinue the

development of the compound. It wasn't until the summer of 2002 that a final decision was made by Mr. White and the PEC to discontinue development of ABT-773.

This concludes my testimony.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 2/17/08, 2008 at Chicago, IL.

2/17 ML  
Jeffrey Marc Leiden, M.D., Ph.D.

**DN**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM: John M. Leonard, M.D.  
DEPT: 432, AP9-1  
PHONE: 847-938-4545  
FAX: 847 937-3918  
DATE: April 27, 2001**

TO: Jeff Leiden                      D-3RD              AP6D

CC: Arthur Higgins              D-309              AP30  
Bob Funck                      D-404              AP9  
Gill Hodgkinson              D-477              AP6A

RE: MONTHLY HIGHLIGHTS – APRIL 2001

**ANALGESIA**

ABT-594

The blind was broken on April 23 for M99-114, our Phase IIb Painful Diabetic Neuropathy study, and the results will be available during the week of April 30th.

**ANTI-INFECTIVE**

ABT-492

Based on PK and safety data from the completed Phase I study (Part I-III), we will continue with Phase I and Phase IIA studies planned for 2001.

ABT-773 (Ketolide)

With the ending of the winter season, Phase III enrollment for CAP (224 actual) and sinusitis (278 actual) are behind projections. Phase III start up activities are nearing completion in Central America for CAP and ABS, and in South Africa and South America for CAP for their winter seasons starting in May. Based on slowing enrollment in the northern hemisphere, we have made the decision to proceed with the enrollment.

A strategic decision analysis process has been initiated with the team to evaluate all options for the ABT-773 dose selection, along with its impact on program timing and cost to be presented to management by the end of May.

The initial Phase I study for the IV formulation is being delayed until July to allow for a protocol amendment to further evaluate dose levels and concentration. We also want to evaluate EKG data obtained from the additional pharmacology study in dog requested by FDA. The timing for a Go/No go decision on the IV formulation will be re-assessed once the new start date has been set.

The CMC and Biopharm End of Phase II meeting is scheduled for May 1<sup>st</sup> and will enable us to present our strategy for bulk drug starting materials, our formulation / bioequivalence plans and drug interaction study results and plans.

**ANTI-VIRAL**

Kaletra

The post approval regulatory commitments due 1Q01 to FDA and EMEA have been submitted.

April 2001 Monthly Highlights  
April 27, 2001  
Page 2 of 2

## DIABETES

### ABT-822 (Bimoclomol)

The Phase IIb study unblinding is approaching. Biorex has issued its final pre-unblinding queries, received and entered >80% of the responses, and locked an initial version of the database. Quintiles is performing an audit of this database the week of April 23rd. Pending the results of this audit, final query resolution, final consistency checks, and patient classification, the unblinding is still scheduled for late the week of April 30.

## ONCOLOGY

### ABT-510

Enrollment of first cohort (3 patients at 100 mg continuous subcutaneous infusion) was completed 4/24

### ABT-518

Enrollment of first cohort (3 patients at 24 mg p.o.) was completed 4/23

### ABT-627

With a successful EMEA meeting on 4/23, we are ready to initiate global Phase III pivotal trials in HRPC.

### ABT-751

The U.S. IND was submitted on 4/23.

## PARD

CMC section of IND application for ABT-751 submitted to Reg. Affairs on target.

Apomorphine – support activities leading to launch in EU are on target.

IDC was successfully inspected by MCA on 02 April 2001. Three minor/other observations and two comments were made.

European patent on Modified Release formulation for Clarithromycin successfully upheld. Time has expired for Hexal AG to file for appeal to the opposition decision.

Significant progress was made in understanding the cause-effect relationship for Kaletra SEC dissolution issue. Additional sampling studies revealed some non-uniformity in drug concentration in the lateral direction in the dissolution flask. Based on these results a new sampling plan has been developed. Release testing has resumed utilizing the new sampling plan. New and stability lots are passing mostly at tier 1 level relieving the tightness in the supply chain. In parallel, exploratory studies continue. A pre-approval supplement, covering a tier 2 method to address the need for cross linked capsules, as well as a new tier 1 method proposal, is targeted for filing during 5/01.

**DO**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM: John M. Leonard, M.D.**  
**DEPT: 432, AP9-1**  
**PHONE: 847-938-4545**  
**FAX: 847 937-3918**  
**DATE: August 10, 2001**

**TO: Jeff Leiden            D-3RD      AP6D**

**CC: Dave Goffredo      D-309      AP30**  
**Ed Ogunro              D-87W      AP30**  
**Bob Funck              D-300      AP30**  
**Tom Lyons              D-404      AP9**  
**Gill Hodkinson        D-477      AP6A**

**RE: MONTHLY HIGHLIGHTS – JULY 2001**

**ANTI-INFECTIVE**

**ABT-773**

- The Decision Analysis process was completed and presented to senior management on July 25<sup>th</sup>, recommending that the Phase III comparator studies for CAP and ABS be conducted with the 150 mg BID dose. We have reached our target of 500 patients enrolled in the ABS QD vs. BID however, and will have the unblinded results available by the end of September to confirm the BID decision.
- The Phase III CAP and ABS study sizes have been increased to improve the chances of obtaining adequate resistant isolates to support our request for a claim for resistance in the label. Also, based on experience gained from the Ketek FDA advisory, we have increased the size of the safety database. Further confirmation of the adequacy of this database will be pursued with the FDA.
- Based on the above changes to the Phase III program, we are re-assessing timelines to the NDA and anticipate a delay beyond the current target of Aug 2002.
- The Phase I QT study protocol is currently being reviewed at FDA and we anticipate written comments from FDA by mid-August.
- An assessment of the Pediatric development to-date was completed, and a proposal to move forward with further formulation development and Phase I studies has been developed. FDA guidelines for a pediatric formulation require companies to show due diligence with a pediatric development program. A pediatric proposal will be made to senior management.
- The Japan development program is progressing with plans being made to initiate an open label study and a BAL tissue study at the end of 2001. At the completion of the open label study in 2002, a meeting with KIKO is planned to present the Phase III plan and address the potential of a bridging strategy.

July 2001 Monthly Highlights  
August 10, 2001  
Page 2 of 2

## **ANTIVIRAL**

ABT-378/r (Kaletra)

**REDACTED**

## **ONCOLOGY**

ABT-627

- The first European Phase III investigator meeting was held July 13-14, and the first three patients were randomized in the M00-244 study.

## **PARD**

## **UROLOGY**

ABT-598 (KCO)

## **DEXMEDETOMIDINE**



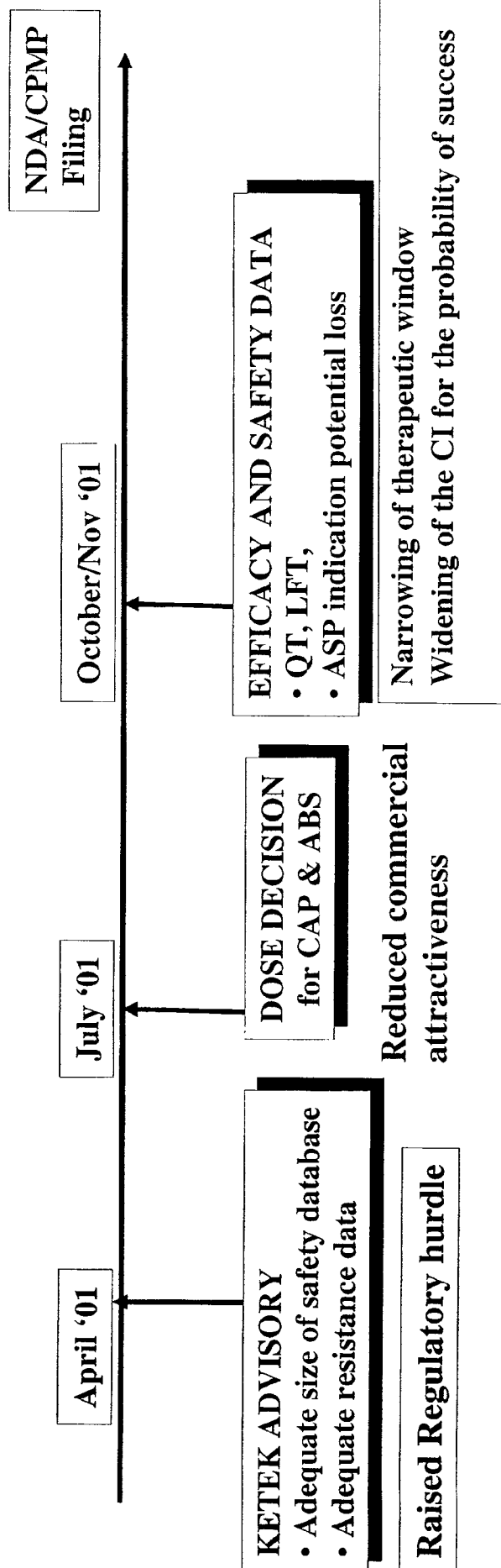
EC

# ABT 773 Agenda

- Update on key developments since the last PEC
  - Ketek FDA Advisory Meeting
  - Dose Decision for CAP and Sinusitis
  - Efficacy and Safety Data
- Impact of key developments on product profile and NPV of the program
- Future options for the program

# ABT 773 Team Summary and Recommendations

Since the April PEC, the development plan has been impacted by:



**Summary: Reducing NPV of the product**

# ABT 773 Target Profile

Target Indications	
Bronchitis	5D
Pharyngitis	5D
Pneumonia	10D
Sinusitis	10D

Attribute	ABT 773	Clari	Levo	Azi	Ketek
<b>QD dosing</b>	ABECB/ASP QD CAP/ABS QD/BID	QD	QD	QD No ABS	QD
<b>Short-duration therapy</b>	ABECB/ ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
<b>Resistance Claim</b>	Pursuing	✖	✓ (15/15 isolates)	✖	Pursuing
<b>Safety</b>	QT, liver, CYP3A	QT and liver liabilities, CYP3A	No safety issues	No safety issues	QT /liver, CYP3A



# Capturing the 2001 winter season drives early BID Dose Decision for CAP/Sinusitis

- Assessed six alternative strategies based on technical, regulatory and commercial attributes

Attribute	ABT 773	Clari	Levo	Azi	Ketek
<b>QD dosing</b>	ABECB/ASP QD CAP/ABS BID w/QD follow on	QD	QD	QD No ABS	QD No ASP US
<b>Short-course therapy</b>	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
<b>Efficacy with resistant organisms</b>	Pursuing 15 isolates Increased to 25 isolates ( ~1500 CAP pts)	Under exploration	✓ (15/15 isolates) 100%	✗	✗ (14/17 isolates) 82%
<b>Safety</b>	QT, liver Added 1000 pts (to achieve BID database ~3200pts)	Approved	Approved	Approved	US ?20 000 pts due to liver/ QT concern, EU approval

# ABT-773 Phase III Efficacy Data to date

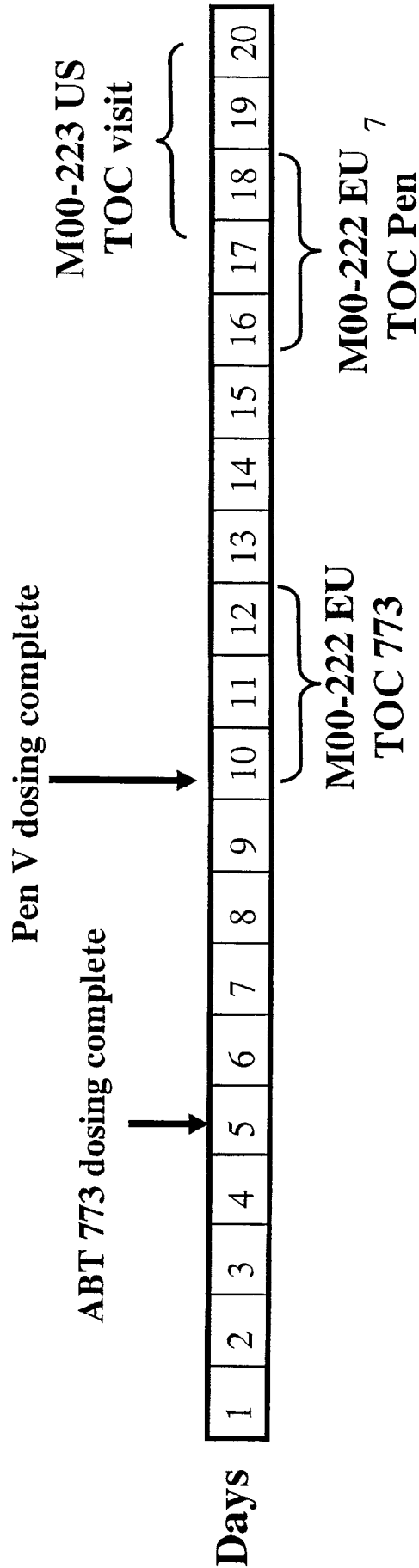
Study	Indication	Comparator	Number ABT-773 Subjects	ABT-773 Dose/ Duration in Days	Status
US, EU (IND) M00-225	Sinusitis	NA	660	150 BID x 10 d 150 QD x 10 d	84-86% interim analysis
US, Canada (IND)	Sinusitis	Augmentin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	Sinusitis	Quinolone	660	150 BID x 10 d	Ready to dose
US (IND) M00-219	CAP	NA	600-800	150 BID x 10 d 150 QD x 10 d	585/600 Unblind Jan
US (IND)	CAP	Levofloxacin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	CAP	Amoxicillin	660	150 BID x 10 d	Ready to dose
US	Pharyngitis	Penicillin	520	150 QD x 5 d	Failed
EU	Pharyngitis	Penicillin	520	150 QD x 5 d	223/520
US	ABECB	Azithromycin	600	150 QD x 5 d	578/600
EU	ABECB	Levofloxacin	500	150 QD x 5 d	327/500

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US: M00-223 (IND study)

ABT-773 150 mg QD VS Penicillin V 500 mg TID  
Streptococcal Pharyngitis/Tonsillitis

- Treatment groups :
  - ABT-773 150 mg on Study Days 1-5
  - Penicillin V 500 mg (250 mg x 2) TID tablets on Study Days 1-10
- 2 different protocol designs for Test-of-Cure (TOC) Visits EU vs US





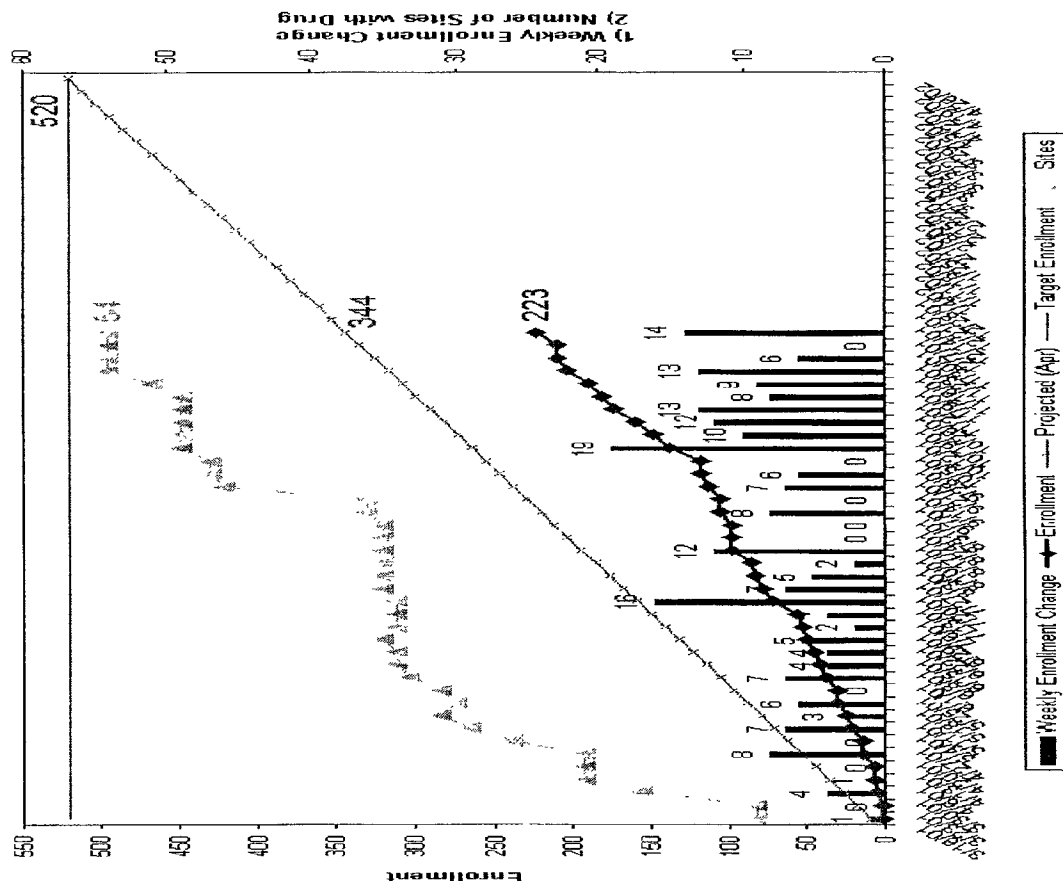
M00-223 US Pharyngitis Study  
Eradication Rate at Test-of-Cure Visit

	ABT-773	Penicillin	95% CI	P-value
<u>Bacteriological</u>				
PP	74% (140/189)	90% (170/189)	(-23.7, -8.0)	<0.001
ITT	64% (141/220)	81% (171/212)	(-25.1, -8.0)	<0.001
<u>Clinical</u>				
PP	85% (160/188)	93% (175/188)		

# Decision that EU ASP Trial continues

M00-222 ASP Study (Ex-U.S. Sites)  
Acute Streptococcal Pharyngitis

- Indication with 150mg QD lost:
  - **US:** Non-approvable, less than 85% bacteriological cure and less than 10% difference
  - **EU:** Likely non-approvable, less than 10% difference to Penicillin and >80% in 2 trials
- Projected enrollment completed Apr 2002.
- Initial results available Aug 2002.



# Pharyngitis and earlier Sinusitis Data are Consistent

- Pharyngitis indication: test of cure is bacteriological  
Sinusitis cure rates 86% BID vs 84% QD based on clinical cure with presumed eradication.
- Indications at different doses;
  - Sinusitis 150 mg QD less effective than 150 mg BID even at 10 days
  - Pharyngitis result findings consistent with clari failure at 5 days and success at 10 days therapy
- Sinusitis had no comparator and will still be tested

## Impact of Pharyngitis Results on Bronchitis Indication at 150mg QD

- Bronchitis trial likely to succeed based on clinical cure rate (blinded clinical rate 82%)
  - Placebo effect
- Bacteriological failure in pharyngitis raises issues of bacteriological efficacy at 150mg QD dose
  - *S. pyogenes* and *S. pneumoniae* have similar MIC profiles
- Bronchitis is only indication left at 150mg QD dose
  - will not be supported by CAP data (occult CAP a clinical concern - EU)

# PART 2





# Impact of pharyngitis data on the product profile

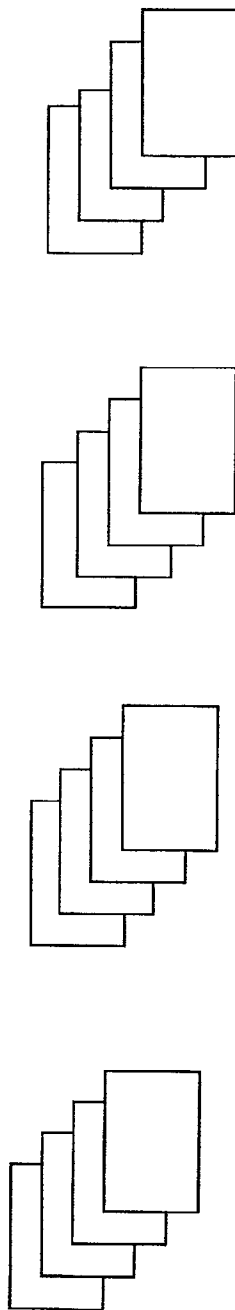
Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	CAP/ABS BID* ASP QD ✖ ABECB QD?	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates Increased to 25 isolates ?	Under exploration	✓ (15/15 isolates)	✖	✖ (14/17 isolates)
Safety database	QT, liver Added 1000 patients ?	Approved	Approved	Approved	US ?20 000 pts due to liver/QT concern, EU approval

•\*Possibility of a QD follow on is limited for all indications.

•ASP 10days and /or BID repeat studies thought to be commercially unattractive

# Safety: M01-325 QT Study Design

- 68 Healthy males and females, 20% greater than 50 years old.
- Double-blind, multiple-dose, four-period crossover each period dosing 5 days, 10 day washout
-  Placebo,  150 mg BID,  300 mg BID,  450 mg BID
- Randomized, into 1 of 4 sequences containing

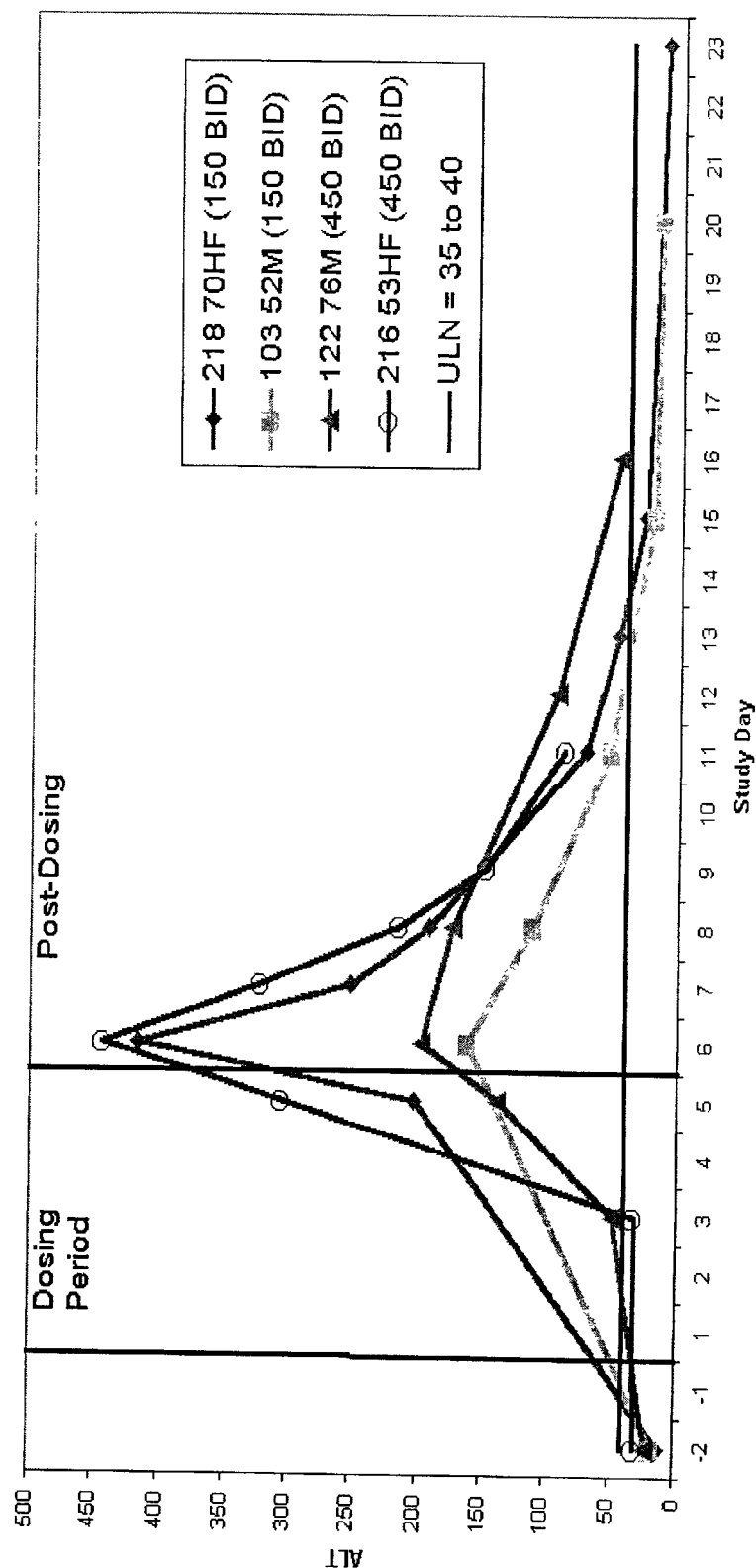


Each period ECG collection:

Day -1 Placebo baseline, Day 1, Day 5 ECG and PK

# Study M01-325: 4 Subjects with Significantly Elevated ( $>3 \times \text{ULN}$ ) ALT (All $>50$ years old)

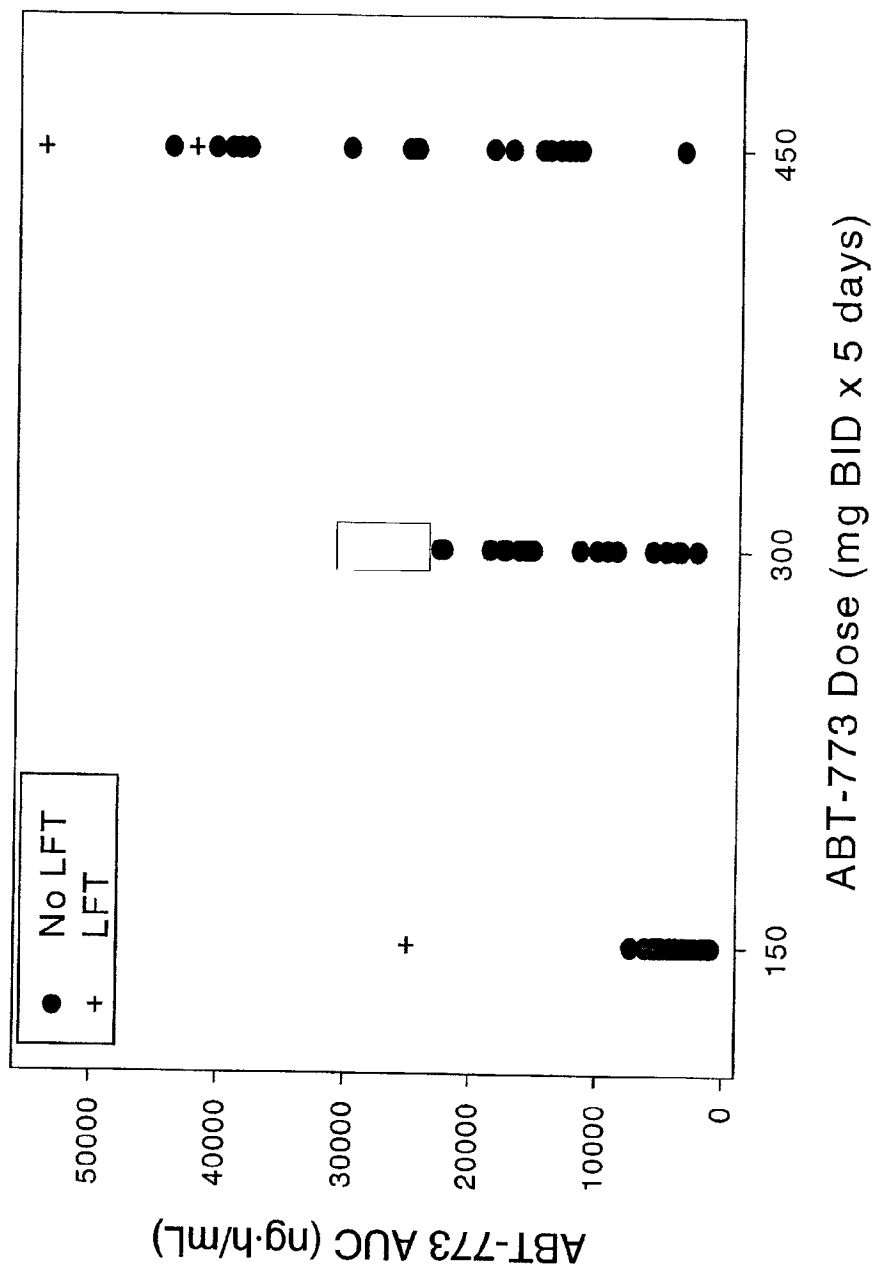
ABT-773, Study M01-325



2 subjects at 150mg BID and 2 subjects at 450mg BID

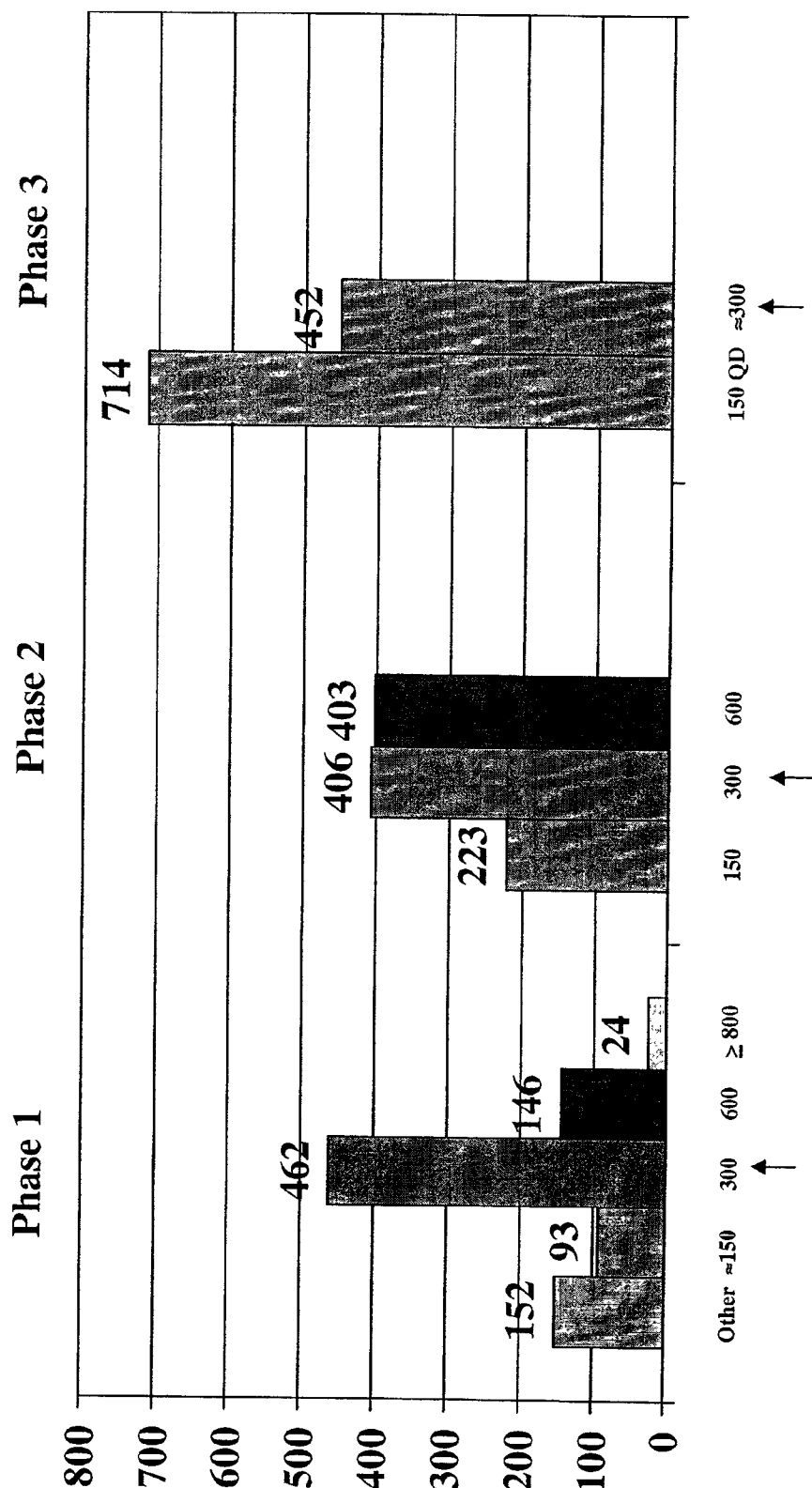


# Study M01-325: Relation Between Dose and Day 5 ABT-773 AUC<sub>0-18</sub>



LFT = Subjects 103, 122, 216 and 218; No LFT = All other subjects.

# No. of Subjects Available for Analysis



Other: single dose or blind data

# Overall Incidence of LFT's Not Changed (All Subjects with LFT)

	$\geq 3 \times$ ULN
Original overall N=2884	39 (1.4%) [1.0, 1.8]
New overall N=2939	43 (1.5%) [1.1, 2.0]
Current Phase 3 N=1047	17 (1.6%) [0.9, 2.6]

**Investigation of the Available Database Exhibits Low  
Concern for Continuing at 150mg BID and 300mg BID  
Overall ALT Abnormality Rates in Phase 2 and 3  
(Normal at Baseline -- ALT <1x ULN)**

	> 1x ULN	≥ 2x ULN	≥ 3x ULN	≥ 5x ULN
<b>150 mg QD</b>	71/738 (9.6%) [7.6, 12.0]	8/738 (1.1%) [0.5, 2.1]	3/738 (0.4%) [0.1, 1.2]	2/738 (0.3%) [0, 1.0]
<b>150 mg BID alone</b>	38/344 (11.0%) [7.9, 14.8]	4/344 (1.2%) [0.3, 3]	1/344 (0.3%) [0, 1.6]	0 [0, 0.8]
<b>300 mg daily (includes 150 mg BID)</b>	88/667 (13.2%) [10.7, 16.0]	8/667 (1.2%) [0.5, 2.3]	3/667 (0.4%) [0.1, 1.3]	0 [0, 0.6]
<b>600 mg daily</b>	59/327 (18.0%) [14.0, 22.6]	8/327 (2.4%) [1.1, 4.8]	2/327 (0.6%) [0.1, 2.2]	1/327 (0.3%) [0, 1.7]

- Only 24 patients at doses 800mg or above
- Dose response demonstrated increases at 600 mg

# ALT Changes at Post-Therapy 1-2 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Clari ER* N=783	ABT-773& 150 mg QD N=574	ABT-773@ 150 mg BID N=328	ABT-773 # 300 mg N=633	ABT-773 ^ 600 mg N=314
>1x ULN	35 (4.5)	50 (8.7)	24 (7.3)	55 (8.7)	39 (12.4)
≥ 2x ULN	3 (0.4)	6 (1.0)	3 (0.9)	6 (1.0)	2 (0.6)
≥3x ULN	0	2 (0.3)	1 (0.3)	2 (0.3)	0
≥5x ULN	0	1 (0.2)	0	0	0

\*Clari ER similar to Clari IR and MR

\*Clari ER Phase 3, ABECB, ABS and CAP

&Phase 2 and 3; @Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

^ Phase 2, including 200mg TID and 600mg QD.

¶ Number (%)

## ALT Changes at Post-Therapy 7-14 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Ketek N=1232*	Comparator N=1031*	ABT-773& 150 mg QD N=618	ABT-773@ 150 mg BID N=302	ABT-773 # 300 mg N=598	ABT-773 ^ 600 mg N=273
>1x ULN	98 (8.0)	92 (8.9)	36 (5.8)	23 (7.6)	46 (7.7)	34 (12.5)
≥2x ULN	6 (0.5)	4 (0.4)	2 (0.3)	1 (0.3)	3 (0.5)	4 (1.5)
≥3x ULN	1 (0.1)	3 (0.3)	1 (0.2)	0	1 (0.2)	2 (0.7)
≥5x ULN	0	0	1 (0.2)	0	0	1 (0.4)

\*Ketek Phase 3

&Phase 2 and 3; @Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

^ Phase 2, including 200mg TID and 600mg QD.

¶ Number (%)

## Maximum ALT Changes in Phase 3 CAP (Ketek, Clari ER, ABT-773)

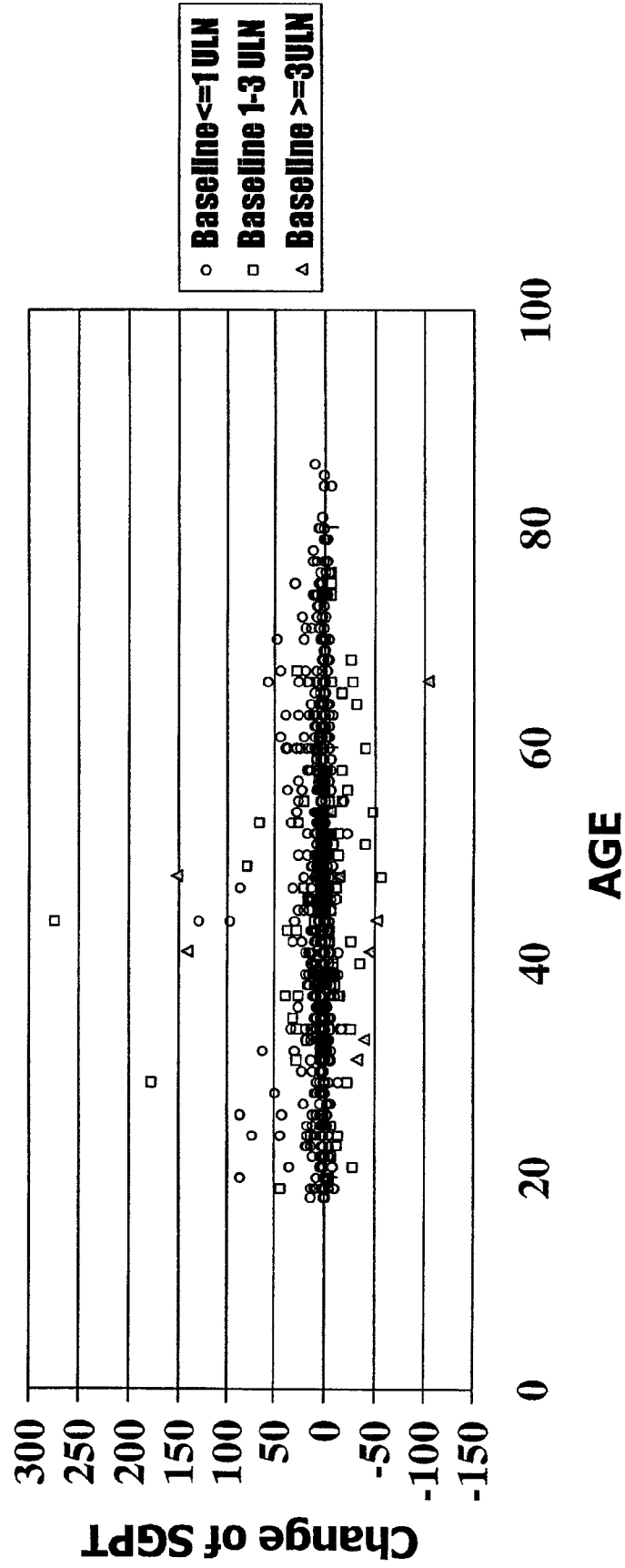
### Studies in Subjects with Normal Baseline Values

ALT Value	Ketek 800 mg QD N=395	Clari ER* 1000 mg QD N=121	ABT-773 150 mg BID N=148
>1x	86 (21.8)	14 (11.6)	17 (11.5)
≥2x	14 (3.5)	5 (4.1)	2 (1.4)
≥3x	4 (1.1)	0	1 (0.7)
≥5x	1 (0.3)	0	0

\* Clari ER similar to Clari IR and MR

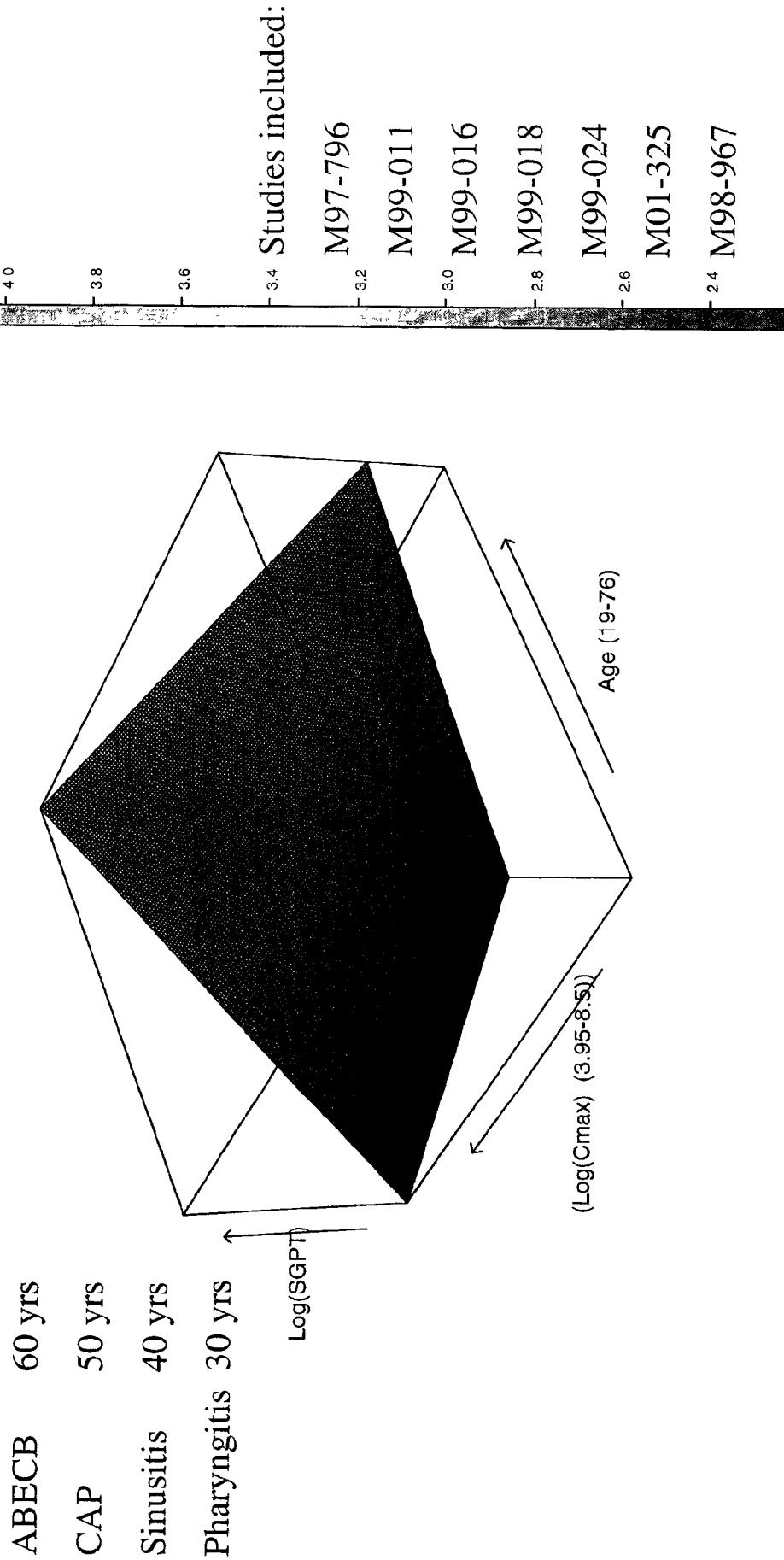
Phase 2/3 (Age Effect)  
Maximum Change from Baseline  
300MG Total Daily Dose

**Change of SGPT vs AGE**





# 3D Model defines relation between hepatotoxicity, dose and age



$$\text{Equation: } \text{Log}(\text{SGPT}) = 2.622678 + \text{Log}(\text{Baseline}) * 0.7179079 - 0.05743167 * \text{age} - 0.2609751 * \text{Log}(\text{Cmax}) + 0.009588997 * \text{age} * \text{Log}(\text{Cmax})$$

## No “Index” Case to Date in ABT-773

- Up to 3% 3x ULN LFTs acceptable in antibiotics  
(CDER-PhRMA-AASLD conference Nov 2000)
- Asymptomatic
- Reversible
- No change in bilirubin (Hy’s law)
- No chronicity

Ketek had 2 index cases

This can drive an increased database need.

Quinolones—6,000 patients

“Hy’s law”—10,000 patients

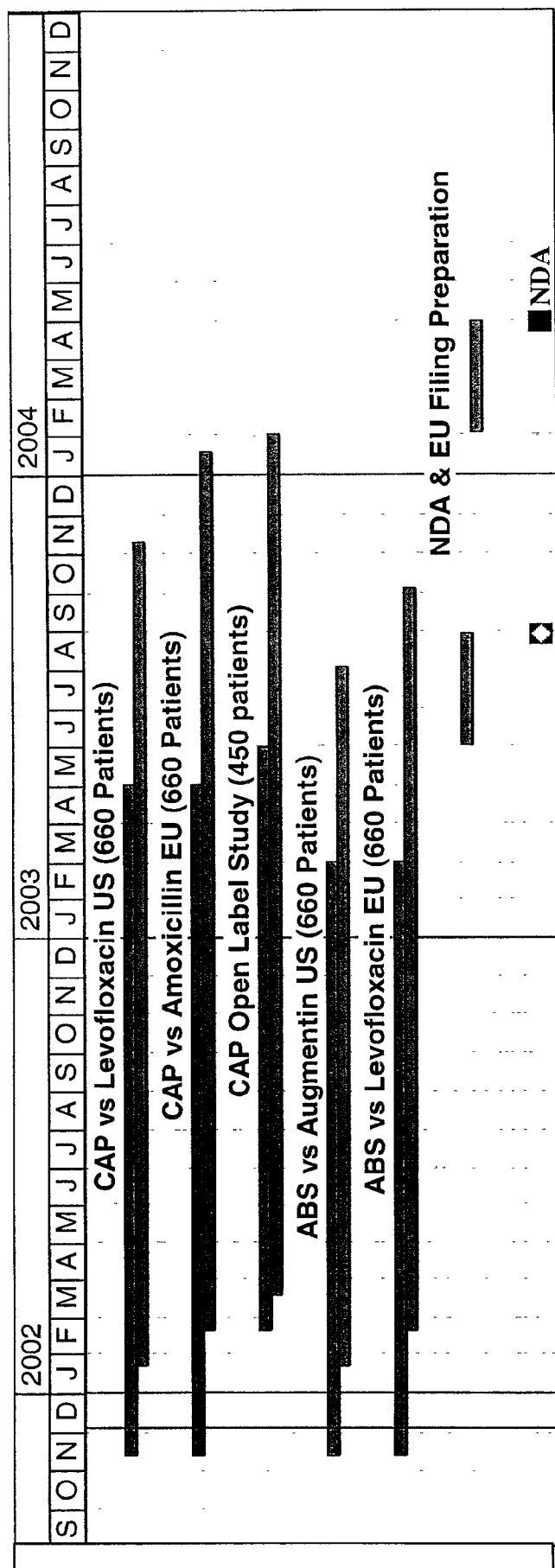
## **Conclusions from Complete Analysis of LFTs**

- Overall average event rate is relatively unchanged
  - 4 cases in QT study
  - (7 cases in Japanese bridging study)
- Definite drug effect with possible greater risk in older individuals and higher doses.
- No. of patients with  $\geq 3$ x ULN ALT within accepted limits for antibiotics at 150mg BID (includes phase 3 trials) (CDER-PhRMA-AASLD conference Nov 2000)
- No ‘index’ case to date
- No single clinical identifier of patients at risk, with possible exception of elderly

## Regulatory Implications of LFT Findings on QT Study and Phase 3 Trials

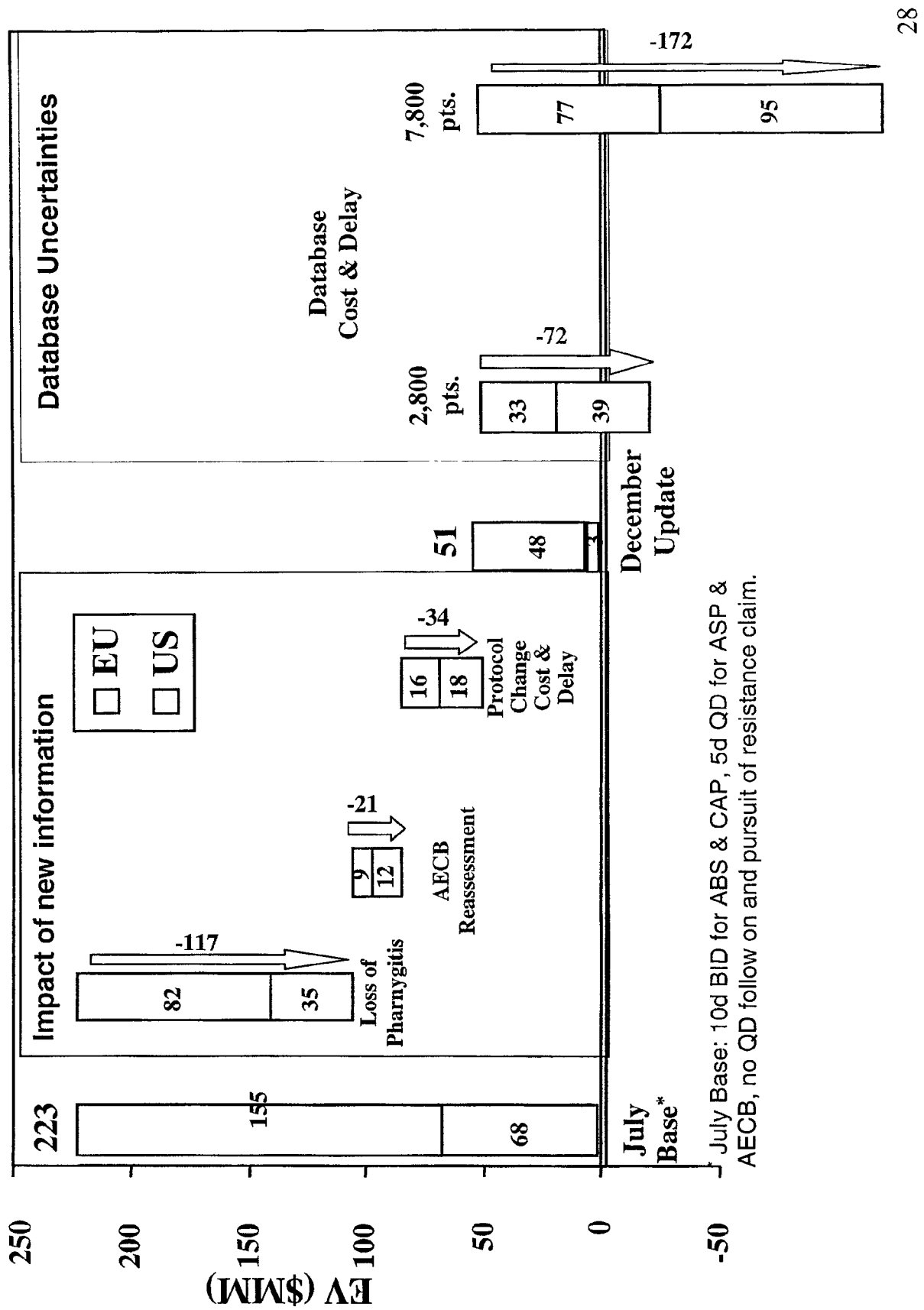
- QT issue still unresolved
  - Proposal to FDA (11/14/01) to recommence QT trial, if practicalities allow and data still acceptable – awaiting response
    - Open label without 450mg BID dose
    - Powering of trial diminished already from patient withdrawals
- LFTs
  - Protocol amendments to add Day 6 LFT monitoring to CAP/ABS trials and changes to informed consent will delay start
  - Amendments to informed consent for ongoing EU pivotals for ASP and ABECB will slow enrollment
  - Notification of dosing suspension of QT study to all regulatory agencies (that require it) has been done
  - Notify all IRB/Ethics Committees of impact

# Impact of Amendments on Phase III Pivotal Studies



\$MM	2002	2003	2004	Total
Current Tablet Budget	68.8	44.2		113.0
Estimate Revised Budget	63.0	53.0	9.0	125.0

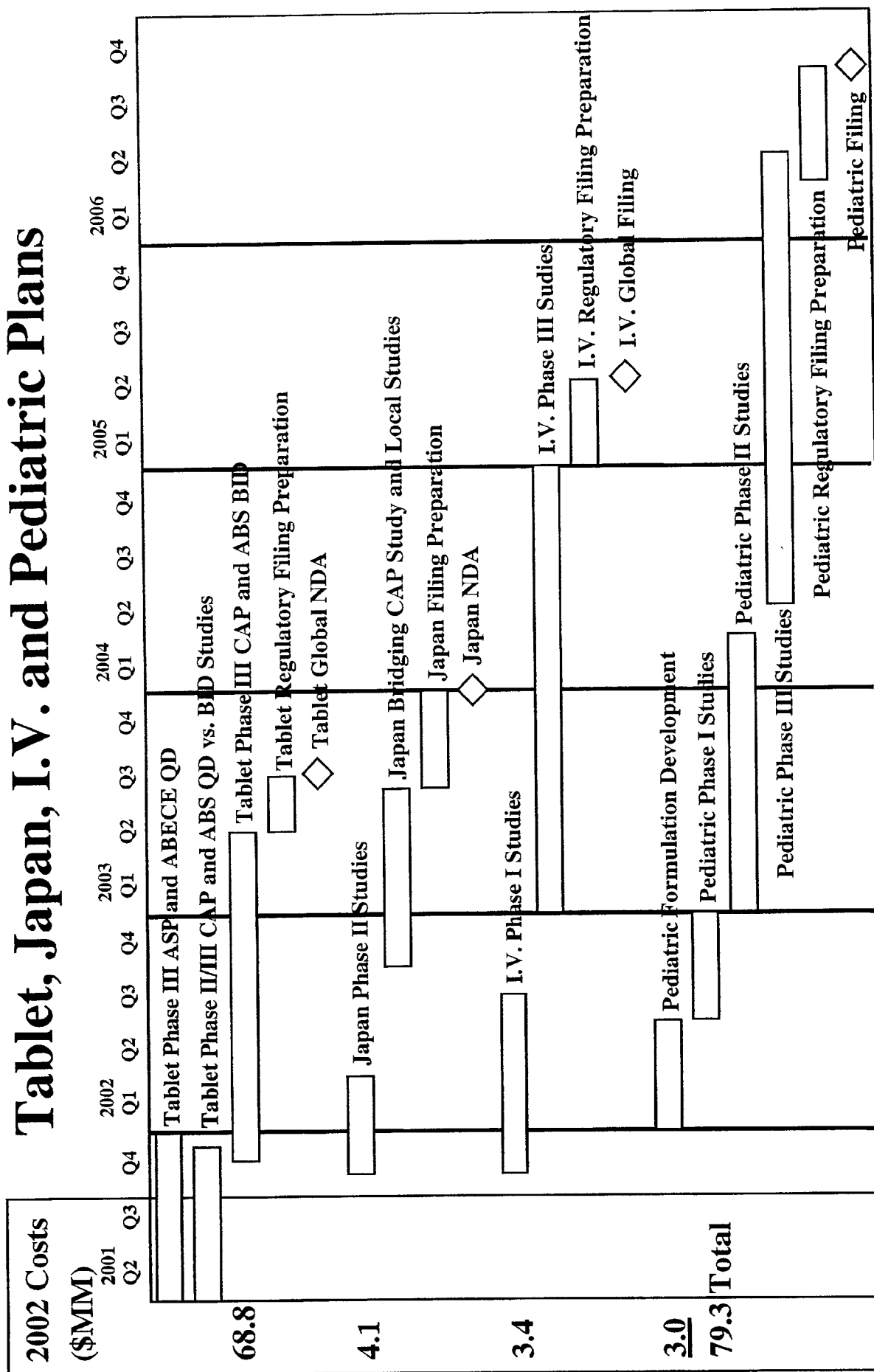
# Value implications of recent ABT-773 information.



Consider exiting ABT 773 Program due to drug profile changes, heightened regulatory risk and lowered NPV

<b>Attribute</b>	<b>Planned</b>	<b>Current</b>
QD dosing	ABECB/ASP QD CAP/ABS QD or BID w/QD follow on	CAP/ABS BID ASP QD ✖ ABECB QD?
Short-course therapy	ABECB/ ASP 5D CAP/ABS 10D	ABECB/ASP 5D CAP/ABS 10D
Efficacy with resistant organisms	Pursuing	Pursuing 15 isolates <b>Increased to 25 isolates ?</b>
Safety database	QT, liver	QT, liver <b>Added 1000 patients</b>
Cost	\$113MM	<b>\$125.0MM</b>
Timeline	Aug 2003	<b>April 2004</b>

# ABT-773 Development Program – Tablet, Japan, I.V. and Pediatric Plans



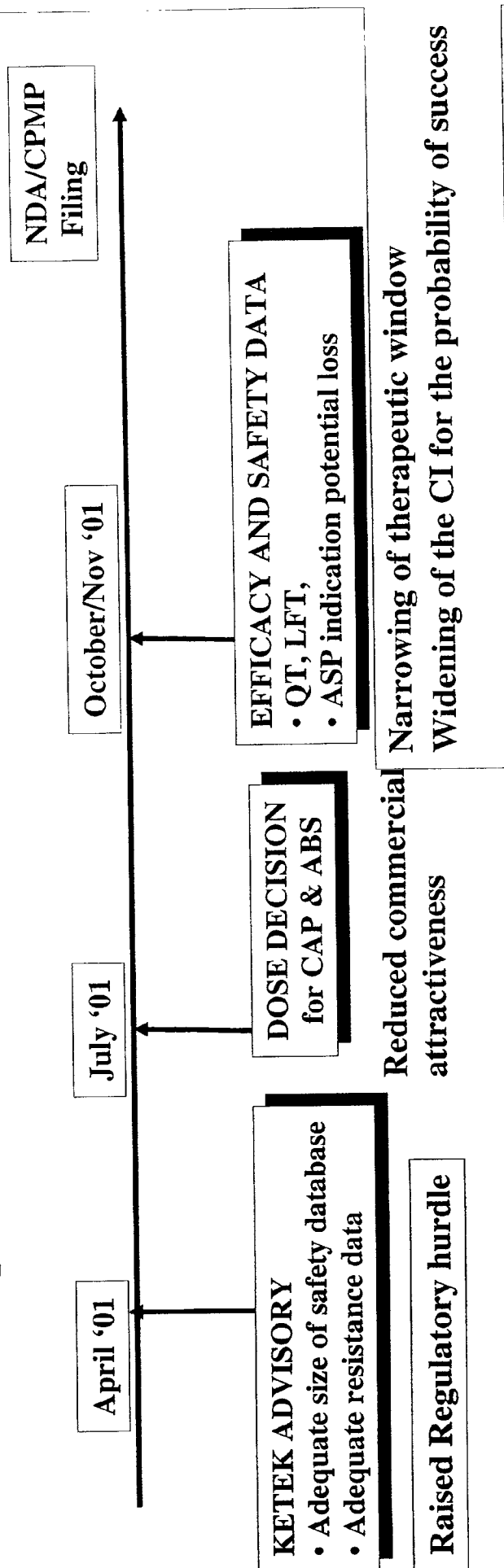


## Japan Impact of ABT 773 Program Developments

- Contractual agreement with Taisho Pharmaceuticals in Japan
- Phase I BAL and Phase II Open Label studies continuing as planned
- QD impact lower in Japan
- Impact of LFT abnormalities needs further evaluation
  - Will be re-assessed at EOP2a KIKO meeting
- Possible bridging strategy is dependent on US/EU filing

# ABT 773 Team Summary and Recommendations

Since the April PEC, the development plan has been impacted by:



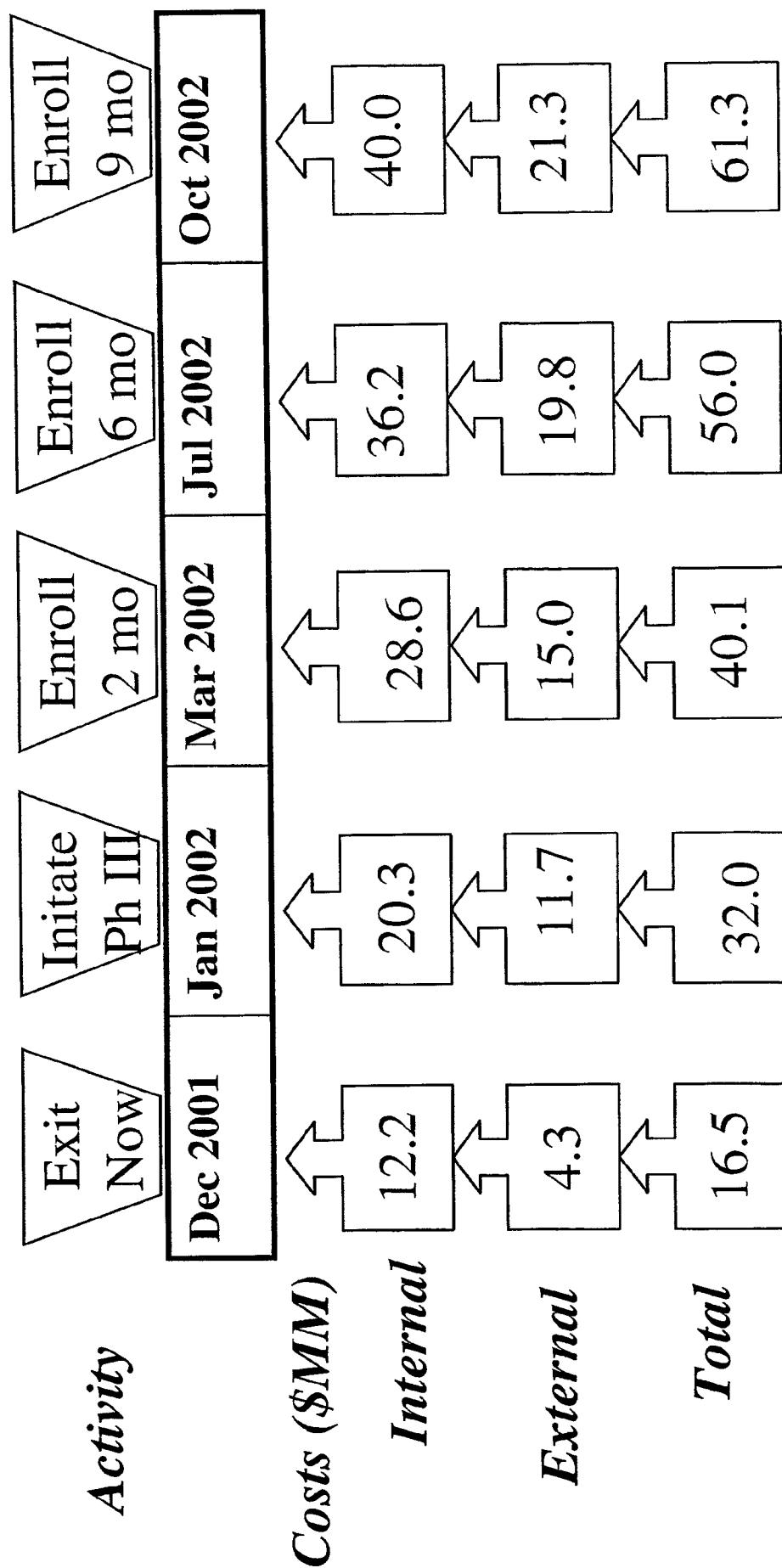
**Summary: Reducing NPV of the product**

**Recommendation: Do not complete development of ABT 773**

# Timing of Actions with Assumptions

Exit Now	Initiate Ph III	Enroll 2 mo	Enroll 6 mo	Enroll 9 mo
<b>Dec 2001</b>	<b>Jan 2002</b>	<b>Mar 2002</b>	<b>Jul 2002</b>	<b>Oct 2002</b>
Close ongoing studies, cancel Phase III pivotals for CAP & ABS. Close IV and Peds development	Submit amendments to IRB/EC and initiate studies as soon as possible.	US enrollment ~150 ABS pts, 80 CAP pts.	US & EU enrollment slowed, end of season, Before So Hemisphere sites started	US & EU enrollment started again, So Hem sites enroll 100 CAP pts.
Avoids majority of external costs in 2002.	Maintain investigator relationships and support. Allow time to plan communication.	Data on ABECB US pivotal study will be available.	Japan KIKO mtg held, ABECB and ASP EU results, Ketolide back up could be ready to start development	Evaluate enrollment achieved and re-assess filing timeline.

# 2002 Exit Costs



2002 Cost assumptions:

- No spending on Peds and IV programs
- Japan clinical costs to KIKO meeting
- 3 mo functional resources and 6 mo clinical resources for shut down activities

# Backups

35

# ABT-773 Adverse Events Phase 2b and Phase 3

Nausea	10% (197/2029)
Diarrhea	9% (192/2029)
Taste	9% (191/2029)
Headache	7% (149/2029)
Vomiting	5% (93/2029)

# ABT-773 Phase III Clinical Plan (Pivotal Trials)

Study	Indication	Comparator	Team recommendations
US, EU (IND) M00-225	Sinusitis	NA	Enrollment has been stopped at 609 patients, close study without open label portion
US, Canada (IND)	Sinusitis	Augmentin	Submit protocol amendment, modify Informed consent, expect approval to start by mid January.
EU (Non-IND)	Sinusitis	Quinolone	Submit protocol amendment, modify Informed consent, expect approval to start by mid February in some countries, remainder in March.
US (IND) M00-219	CAP	NA	Enrollment has been stopped at 586 patients, close study.
US (IND)	CAP	Levofloxacin	Submit protocol amendment, modify Informed consent, expect approval to start by mid January.
EU (Non-IND)	CAP	Amoxicillin	Submit protocol amendment, modify Informed consent, expect approval to start by mid February in some countries, remainder in March.
US	Pharyngitis	Penicillin	Failed
EU	Pharyngitis	Penicillin	Continue enrollment (currently 209) to meet targets by end April 2002. Modify informed consent.
US	ABECB	Azithromycin	Enrollment target will be met by 12/5/01
EU	ABECB	Levofloxacin	Continue enrollment (currently 327) until target of 500 patients is met at end March 2002. Modify informed consent.

# Overall Incidence of LFT's Not Changed (All Subjects with LFT)

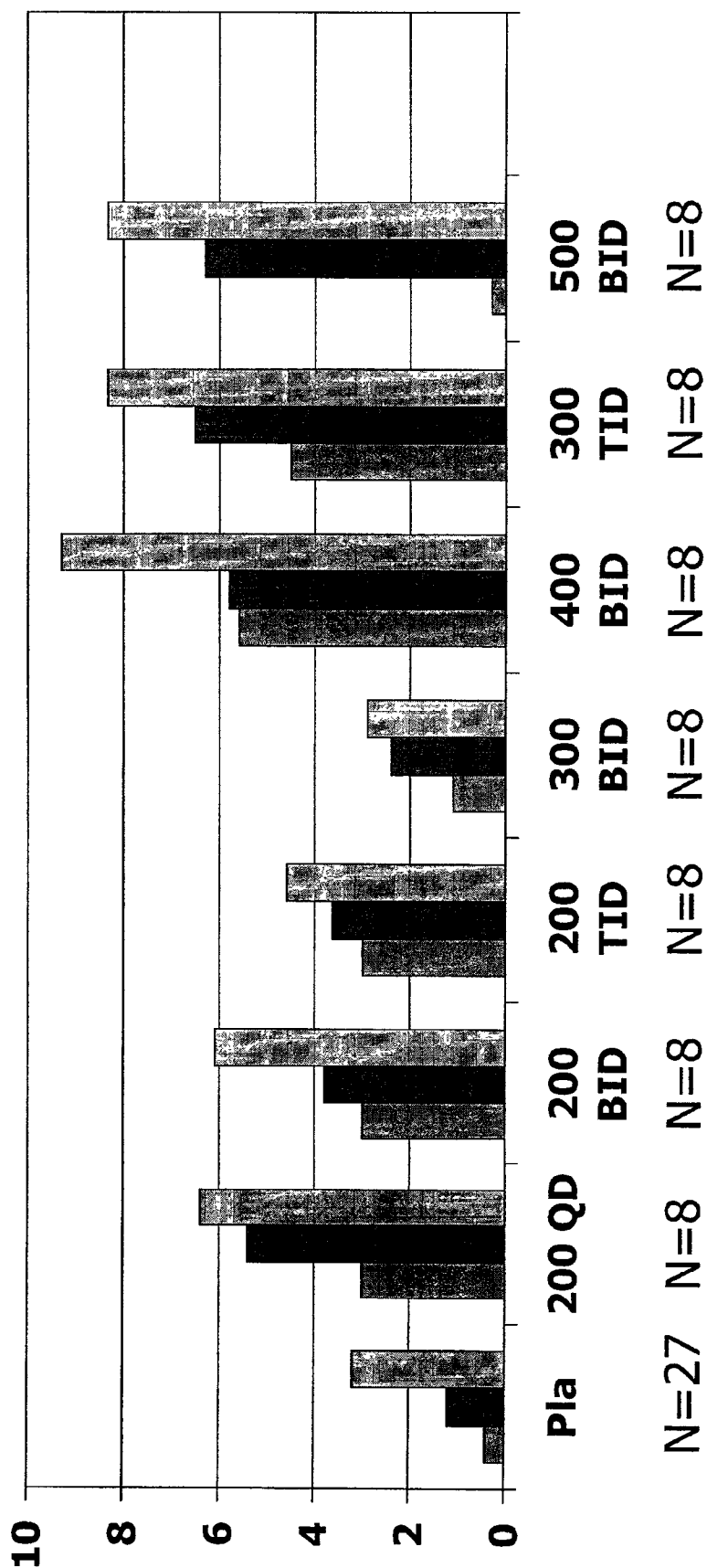
	$\geq 3 \times ULN$ Study			
	Normal Baseline $< 1 \times ULN$	Abnormal Baseline $1-3 \times ULN$	Significantly Abnormal Baseline $\geq 3 \times ULN$	Total
Original overall N=2884	13	17	9	39 (1.4%) [1.0, 1.8]
New overall N=2939	17	17	9	43 (1.5%) [1.1, 2.0]
Current phase 3 N=1047	4	7	6	17 (1.6%) [0.9, 2.6]



# Multiple Rising Dose Study (M97-796)

## Mean Change from Baseline in SGPT

■ During Treatment ■ 24 hour post dosing ■ 48 hour post dosing



# Timing of dosing does not make a difference

Shift Tables of SGPT in 300 mg Total Daily Dose in Phase 2 and 3

Studies	$>1*ULN$	$\geq 2*ULN$	$\geq 3*ULN$
M99-048 (5 days) AECB	10.9% (11/101)	1.7% (2/117)	2.5% (3/120)
M99-054 (7 days) CAP	26.1% (18/69)	5.1% (4/78)	2.5% (2/80)
M00-219 (10 days) CAP	11.5% (17/148)	3.5% (6/172)	1.7% (3/176)
M99-053 (10 days) ABS	10.5% (9/86)	1.1% (1/95)	0.0% (0/95)
M00-225 (10 days) ABS	10.8% (21/195)	1.9% (4/213)	0.5% (1/216)

## ABT 773 QT issues

- Re-read key Phase I and Phase II ECG data (6749 ECGs)-completed
- Phase III studies ECGs: Ongoing studies (9085 expected)-45% completed  
Planned studies (8000 expected)
- Dedicated Phase I QT evaluation study as agreed by FDA started Sept 01 (>9000 ECGs)
  - Four-period, double-blind, placebo-control crossover designTime-matched ECGs/PK samples at day-1, day1 and steady state on day 5

**TOTAL OF 34000 ECG's: Most with correlating plasma levels of ABT773**

# Regulatory experience defined new regulatory standards which determines program size:

- Size of the safety database is driven by the product **benefit/risk** profile:
  - Ketek's 3200 patient safety database insufficient, ?liver/QT.
- A resistance claim will significantly support benefit risk:

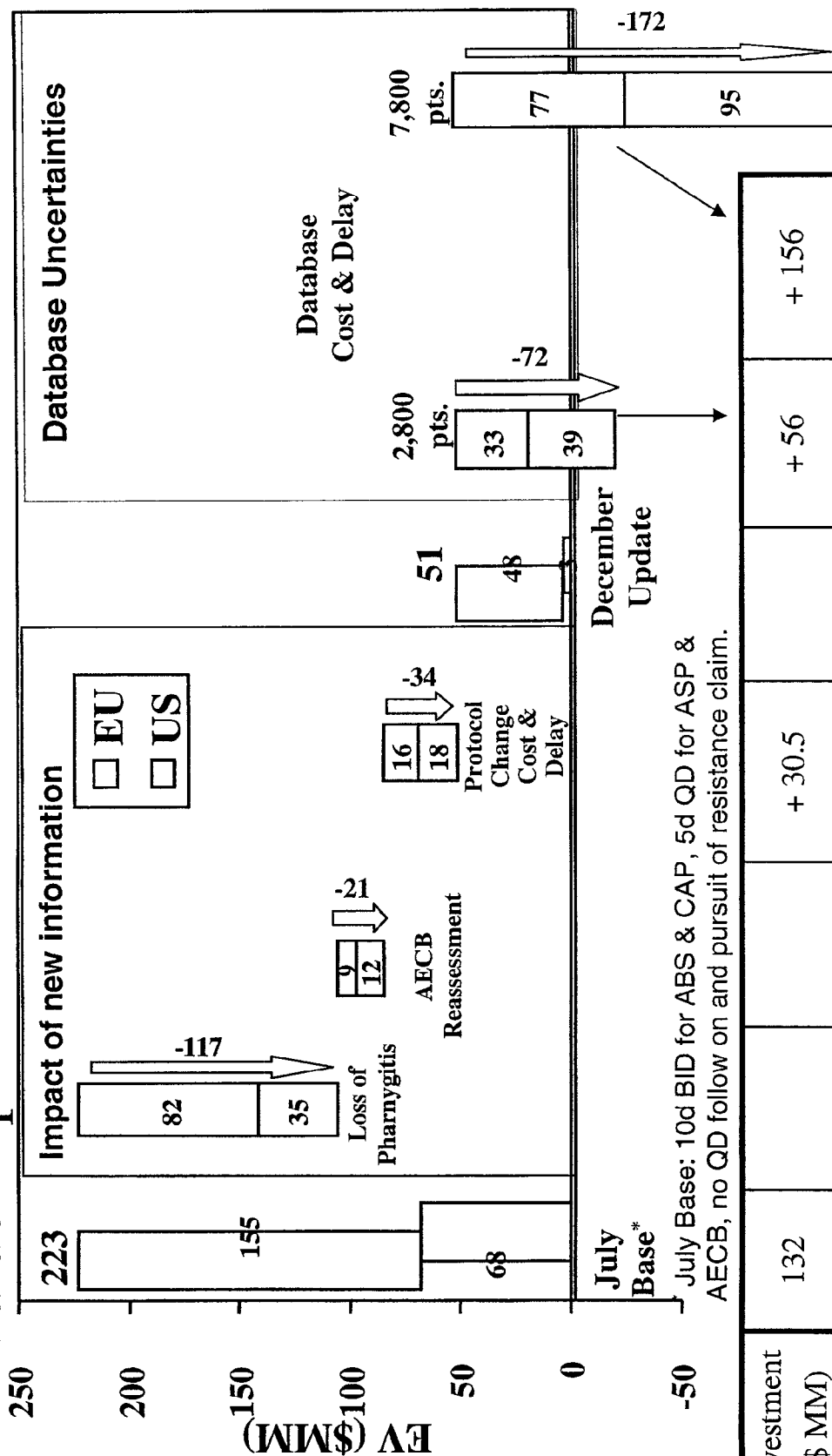
Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	1563	781
30	2182	1875	938

- Importance of CAP emphasized

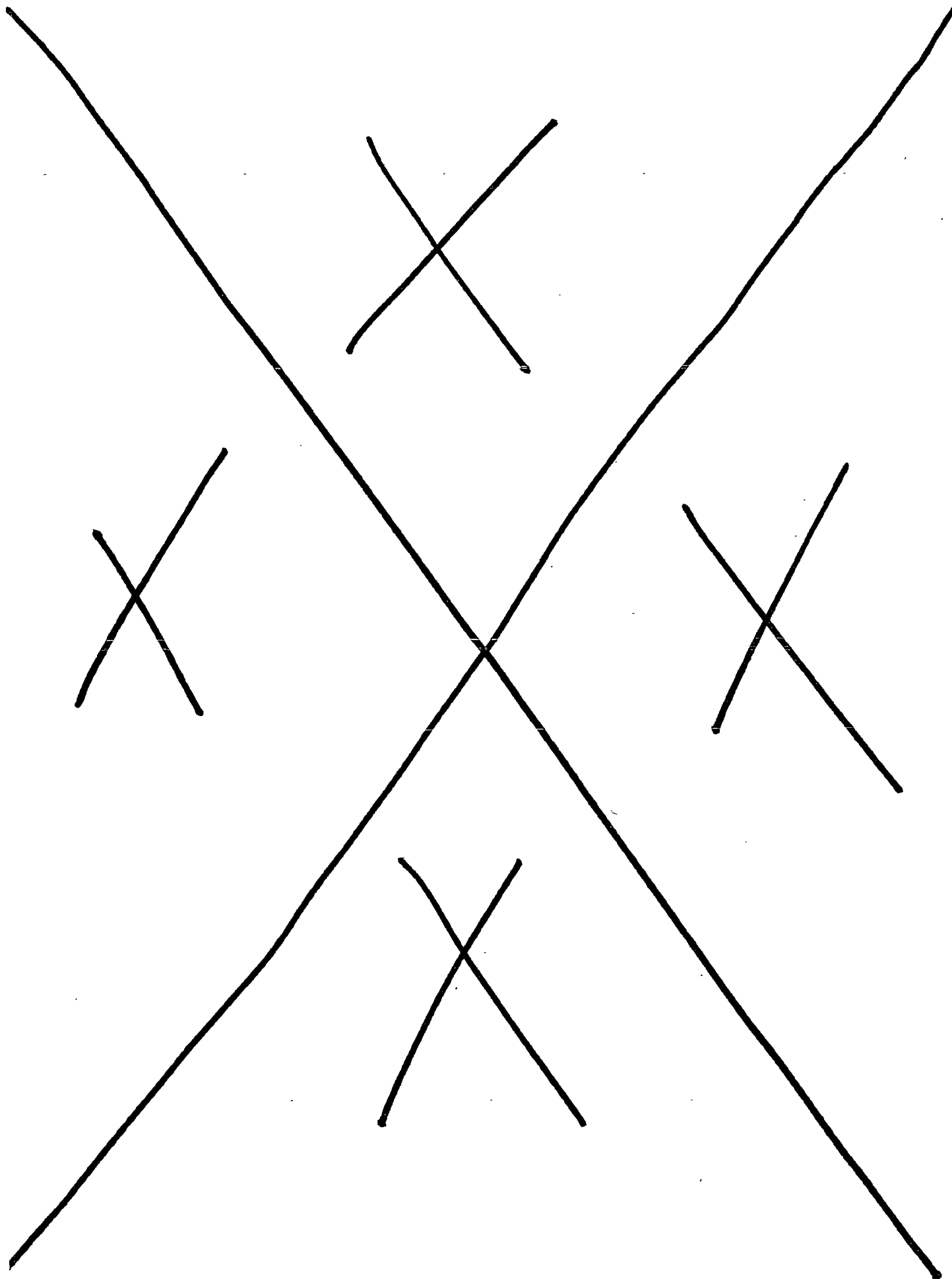
Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

1. Complete current ABS & CAP dose-ranging trials and then make dose decision. (Use ABS & CAP dose-ranging data)
2. Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. (Use ABS dose-ranging data only)
3. Select the BID dose today for ABS & CAP Ph III pivotal. (Select BID today)
4. Select the QD dose today for ABS & CAP Ph III pivotal. (Select QD Today)
5. Develop BID in CAP & ABS for EU; Develop QD for US. (QD in the US & BID in the EU)
6. Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator. (Phase III 3-arm CAP & ABS pivotal). Variation: drop arm on result availability

## Value implications of recent ABT-773 information.



Investment (\$ MM)	132			+ 30.5		+ 56	+ 156
Launch Date	4Q04			4Q05		4Q06	4Q07
Expected Peak Sales (\$ MM)	Total	312	248	235	235	235	235
	US	168	145	137	137	137	137
	EU	145	103	99	99	99	99







# Operations Highlights

September 7, 2001  
Board Meeting

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ABBT0577959

## Pharmaceutical Products Division Highlights



- **Anti-Infective** – Continue Biaxin life cycle management  
REDACTED
  - Biaxin XL received FDA approval for Community-Acquired Pneumonia
  - Omnicef co-promotion agreement  
REDACTED
- **Urology/Cardiology** – Increase commercial presence in Cardiology.  
REDACTED
  - Addition of 100 sales representatives to promote TriCor
  - Expansion of Mavik (ACE inhibitor) and Tarka (ACE/Calcium blocker combo)
  - Flomax  
REDACTED

## Pharmaceutical Products Division Highlights

**Commercial** (cont.)

- HIV – Focus on the use of Protease Inhibitors in earlier AIDS treatment regimens.
  - Kaletra continues to grow, REDACTED
  - Abbott is now the #1 protease company
- Diabetes / Metabolism
  - Submitted the Synthroid NDA to the FDA on August 1, 2001, REDACTED
  - The Direct-to-Consumer advertising used by Knoll for Meridia
- Immunology – Establish Abbott as a premier company in rheumatoid arthritis
  - D2E7 development program
  - Pre-marketing activities REDACTED
  - Projected peak year sales of D2E7

## Pharmaceutical Products Division Highlights

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### Operational

- US Knoll integration continues on track with several key milestones achieved.
  - An Immunoscience drug development center of excellence
  - The Mt. Olive headquarters
  - Knoll's business system, SAP,

REDACTED

### R&D

- The clinical development of ABT-627, (Atrasentan) for prostate cancer is continuing on schedule. Two pivotal Phase III trials have recently been initiated.
- Based upon experience gained from HMR's Ketek FDA advisory meeting, the size of ABT-773 (Ketolide antibiotic) safety database has been increased. This will result in a one year delay in the filing of ABT-773.

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## Abbott Portfolio Review

March 7-9, 2001

- 
- Project: NNR
  - Compound: ABT-594
  - Presenter: Bruce McCarthy, MD

Revised 04/14/2001 1:14 PM dls... as: lars@pioneer.com - 04/20/01

## ABT-594 Project Team Members

- |                    |  |
|--------------------|--|
| ◆ Venture          | Bruce McCarthy, Michael Biarnesen,<br>Marilyn Collicott, Aldona Matalonis, Alyssa<br>O'Neill |
| ◆ Statistics       | David Morris, James Thomas, Yiming<br>Zhang  |
| ◆ Commercial       | Laura Robinson, Lisa Lux   |
| ◆ Pharmacokinetics | Walid Awni, Sandeep Dutta  |
| ◆ Discovery        | Mike Meyer, Jim Sullivan   |
| ◆ PARD             | Howard Cheskin, Lloyd Dias, David Stroz  |
| ◆ SPD              | Jim Ciullo   |
| ◆ Metabolism       | Joe Machinist, Stan Roberts  |
| ◆ Toxicology       | Bill Bracken, Julia Hui  |
| ◆ Regulatory       | Jim Steck, David Ross, Nigel Livesey   |

Revised 04/14/2001 1:14 PM dls... as: lars@pioneer.com - 04/20/01

## ABT-594 Target Indication

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

### Upside Claims

- ◆ Neuropathic Pain
- ◆ Post herpetic neuralgia
- ◆ OA Pain
- ◆ Chronic Pain
- ◆ Cancer Pain

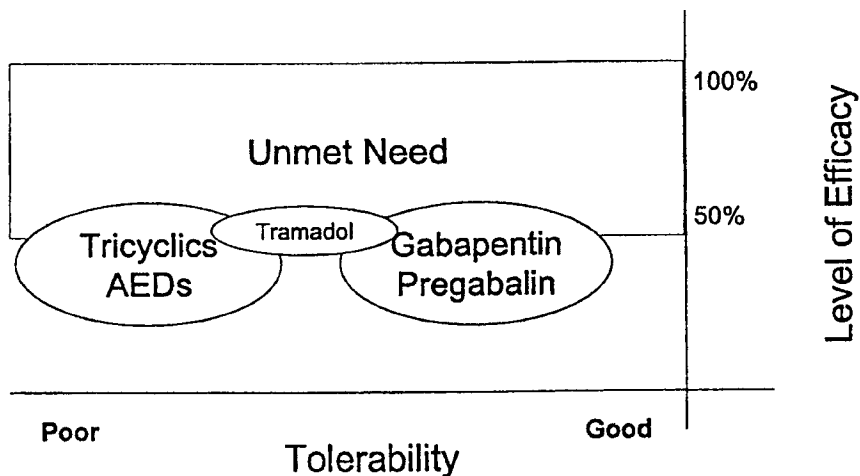
### General Pain Claim

- ◆ Not viable due to 1.5 hour onset

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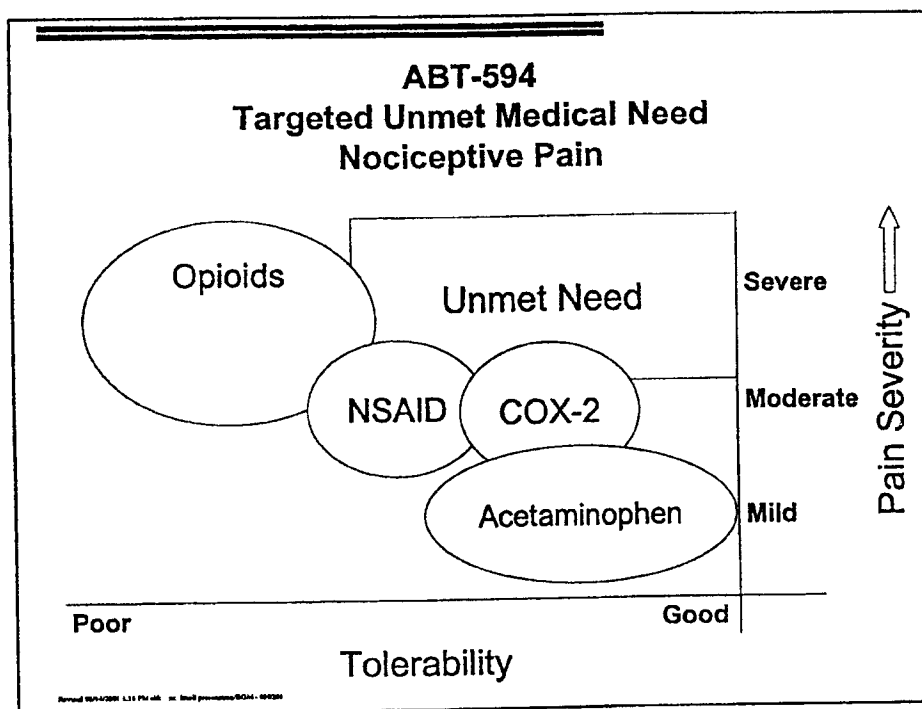
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## ABT-594 Targeted Unmet Medical Need Neuropathic Pain



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**ABT-594**  
**Targeted Product Profile**

	ABT-594 TARGET PROFILE	Current Gold Standard Gabapentin (Neurontin)
Efficacy	> 40% Average Pain Reduction	39% Average Pain Reduction
Side Effects	< 20% Nausea, Vomiting, Dizziness (during titration)	Somnolence: 23% Dizziness: 24% Confusion: 8% Nausea: 8%
Dosing	BID	TID
Other		Not Labeled for Pain

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## ABT-594

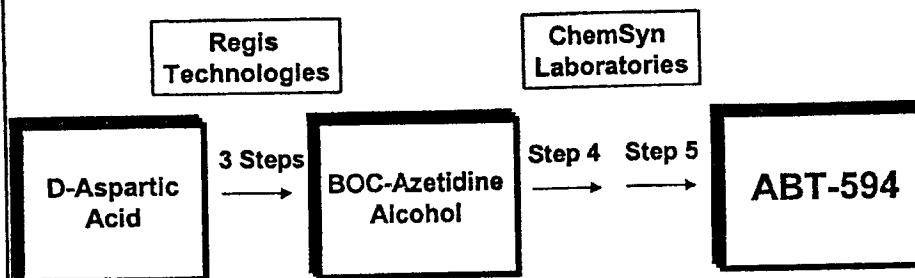
### ◆ Key pre-clinical findings:

- Pharmacology
  - Effective across preclinical models of acute, persistent and neuropathic pain
  - Retains efficacy upon repeated dosing
  - Analgesia via activation of neuronal nicotinic receptors (NNRs) and not via opioid receptors
  - Morphine-like side effects unexpected
    - Constipation
    - Respiratory depression
    - Sedation
- PK/metabolism in animals
  - No CYP interaction
  - No significant metabolism
- Toxicology
  - No issues identified

Revised 06/14/2007 1:10 PM (ABT-594) - see final presentation/SCM - 000000

## ABT-594

### ◆ Chemistry and Manufacturing: Drug Substance (Ebanicline Tosylate)



Commercial Cost Estimate: \$20,000 / Kg Tosylate Salt  
(\$40,000 / Kg Base Equivalent)

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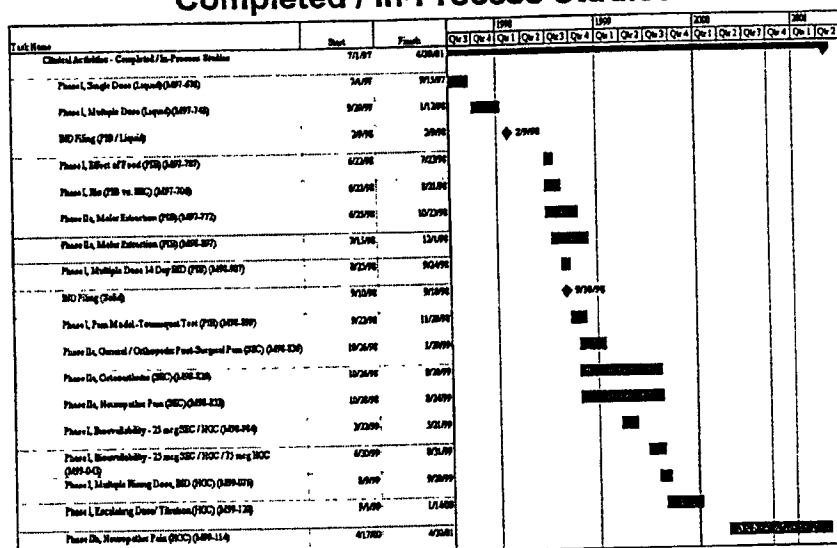
## ABT-594

### ◆ Chemistry and Manufacturing: Drug Product

- Hard Gelatin Capsules
- Dosage strengths: 75, 150, (25)  $\mu$ g Base eq.
- Site: Abbott Puerto Rico
- Manufacturing process:
  - Drug is dissolved in hydro-alcoholic solution
  - Solution sprayed onto micro-porous excipient in a high-shear mixer
  - Granulation is dried, blended with excipients and encapsulated into hard gelatin capsules

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## ABT-594 Global Clinical Development Plan Completed / In-Process Studies



Revised 05/14/2008 1:10 PM alt... -00 Inval process=00001 - 00001



## ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies, Gantt 1 of 2

Task Name	Start	Finish	2001				2002				2003			
			Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4
Clinical Activities - Planned / Proposed Phase I Studies	2/28/01	6/30/03												
DMN / Human Form Model	2/28/01	9/28/01												
Human Metabolism Study	2/28/01	5/30/01												
GI Absorption	2/28/01	5/28/01												
Japan, Single Dose / Multiple / Food Effect	2/4/02	10/3/02												
Human Abuse Liability	2/4/02	2/3/03												
Interaction #1 (Digoxin)	2/4/02	3/6/02												
Interaction #2 (Rifampin)	2/4/02	3/6/02												
Interaction #3 (Ketoconazole)	2/4/02	3/6/02												
Interaction #4 (Midazolam)	2/4/02	3/6/02												
Interaction #5 (Dextromethorphan)	2/13/02	11/13/02												
Interaction #6 (Antacid/H2PT)	2/13/02	11/12/02												
Interaction #7 (Carbamazepine or Oral HD)	2/13/02	11/12/02												
Interaction #8 (Morphine)	2/13/02	11/12/02												

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## ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies, Gantt 2 of 2

Task Name	Start	Finish	2001				2002				2003			
			Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4	Qtr 1	Qtr 2	Qtr 3	Qtr 4
Clinical Activities - Planned / Proposed Phase I Studies	2/28/01	6/30/03												
Interaction #9 (TRD: Anti-spasmodic or tricyclic)	2/13/02	11/12/02												
Interaction #10 (TRD: Vom, Colicoid or Alkaloid)	2/13/02	11/12/02												
PK - Renal Impaired	2/4/02	2/3/03												
PK - Simultaneous / Non-simultaneous Use	2/4/02	2/3/03												
PK - Overdose	2/4/02	2/4/03												
PK - Pediatric	2/4/02	2/4/03												
PK - Hepatic Impaired	2/4/02	2/3/03												
PK - Diabetic Gastroenteritis	2/13/02	6/30/03												
PK - Cardiovascular Safety	2/13/02	6/30/03												
Definitive Bio - Food Effect	2/4/02	2/4/03												
Definitive Bio - Phase II / Phase III / Commercial	2/4/02	6/5/02												
Definitive Bio - Different Strengths	2/4/02	2/5/02												

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## ABT-594 Global Clinical Development Plan Planned & Proposed Phase II, III & IV Studies

[illegible]

Received 2004-09-14; revised 2004-11-10; accepted 2004-12-01.

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## ABT-594 Development Budget

(\$MM)	2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
<b>Base Program</b>						
CMC						
- PARD	1.1	2.8	6.2	5.2	3.2	1.0
- SPD	0.1	1.0	1.0	1.0	1.0	1.0
Drug Safety	1.4	0.9	2.3	1.7	0.9	0.5
Other:	1.2	0.5	1.2	-	-	-
<b>Base Program Total</b>	<b>3.8</b>	<b>5.2</b>	<b>10.7</b>	<b>7.9</b>	<b>5.1</b>	<b>2.5</b>
<b>Clinical Program</b>						
Venture Management	4.0	0.2	6.6	6.6	6.0	5.0
Data Mgmt / Stats	0.5	0.2	5.5	7.5	4.7	2.0
Clinical Grants	1.1	0	36.8	33.7	6.0	2.0
<b>Clinical Program Total</b>	<b>5.6</b>	<b>0.4</b>	<b>48.9</b>	<b>47.8</b>	<b>16.7</b>	<b>9.0</b>
<b>Annual Total Costs</b>	<b>9.4</b>	<b>5.6</b>	<b>59.6</b>	<b>55.7</b>	<b>21.8</b>	<b>11.5</b>

Revised 09/02/2004 1:16 PM:alt... by: David Greenman/DOH - 02/20/04

■

## **ABT-594**

### **◆ Summary of Phase I findings**

- Half-life ( $t_{1/2}$ ): 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{max}$  similar with/without food
- $T_{max}$  may vary somewhat with formulation, food
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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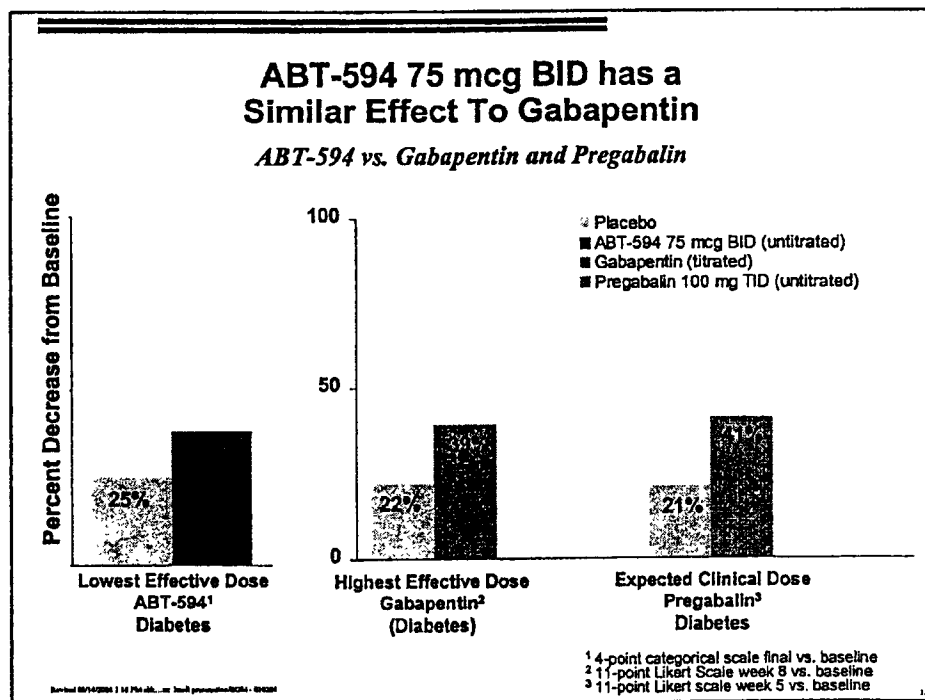
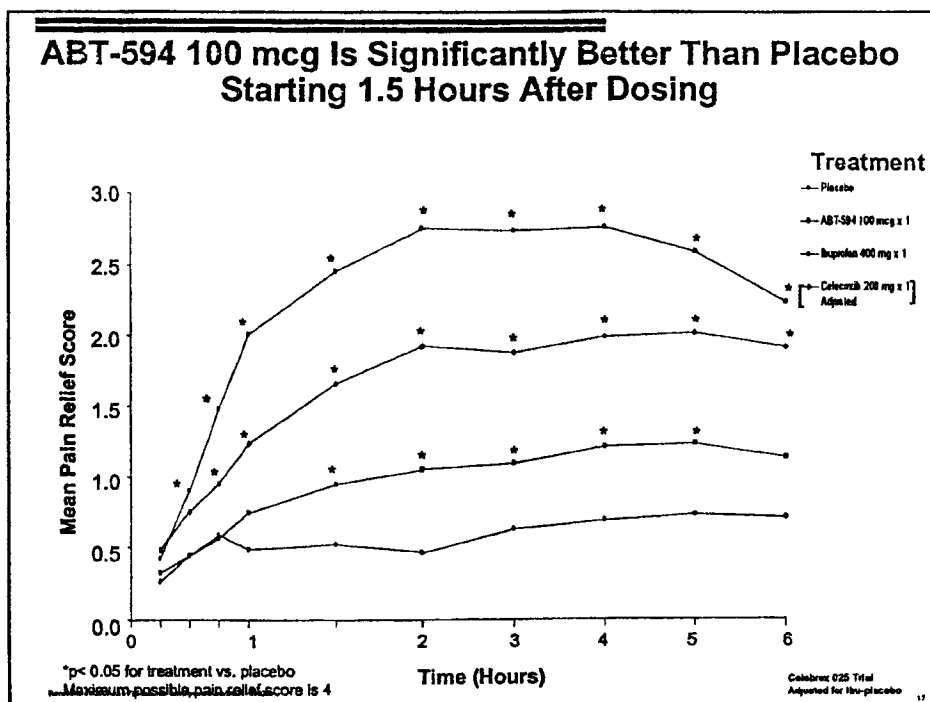
## **ABT-594**

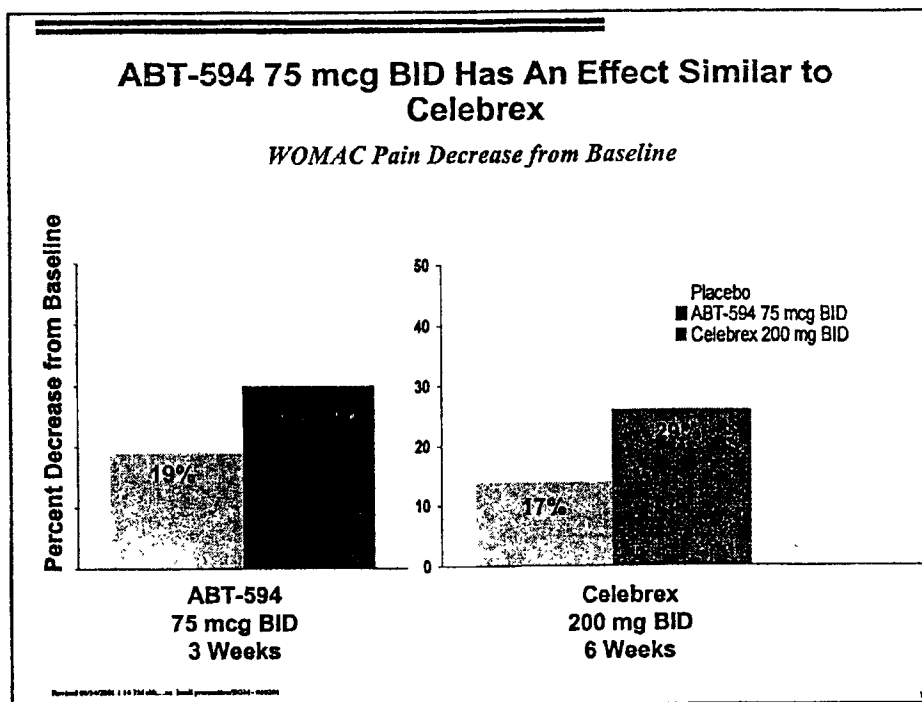
### **◆ Summary of Phase IIa findings**

- ABT-594's analgesic potential demonstrated in:
  - Molar Extraction
  - Neuropathic Pain
  - Osteoarthritis
- Well tolerated in chronic Phase IIa studies
  - 75 mcg BID maximum dose
- Limited additional Phase I data suggested re-evaluation of efficacy at higher doses

Revised 06/14/2005 1:14 PM vlt...at: last promotion/0204-010001

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### Adverse Event Rates for ABT-594 and Select Analgesics

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

<sup>1</sup> Max, 1987 (n=29)

<sup>2</sup> M98-826 and M98-833 combined

N/A - Not Available

Revised 09/14/2006 1:14 PM dls... no final presentation/0204 - 00000

### Adverse Event Rates for ABT-594 and Select Analgesics

Event	Ultram <sup>1</sup> 50-100 mg q4-6h	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12h	ABT-594 <sup>3</sup> 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)<sup>2</sup> "Clinical trials" (label)<sup>3</sup> M98-826 and M98-833 combined

N/A - Not Available

[illegible]

—

# ABT-594

### ◆ Summary of Phase IIb Plans

- Neuropathic Pain
  - Improved study design
  - 150, 225, 300 mcg BID
  - Data available 5/2001
- Osteoarthritis
  - Blue plan
- Tolerability evaluation
  - Rate of rise impact
  - Titration

Received 09/04/2008 1:15 PM; revised 10/01/2008 09:02 AM; accepted 10/01/2008 09:02 AM.

## ABT-594

### ◆ Regulatory status:

- USA, Canada
  - IND 56,980, solid oral dosage form - Division of Anesthetic, Critical Care, and Addiction Drug Products (1998)
  - IND 55,293, oral solution - Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (1998)
  - Informal Teleconference with FDA, August 26, 1998 (incl. John Hyde, MD)
  - End of Phase II meeting planned, October 2000
- Europe
  - Phase I studies conducted, no regulatory interactions
  - End of Phase II meeting planned, October 2001
- Japan
  - No activity

Revised 05/04/2004 1:14 PM ed... for final presentation/SCM - 01/0004

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## Strategic Summary

## ABT-594

### ◆ Key Project Strengths / Positives

- Product attributes
  - Orally available
  - May be effective for neuropathic and nociceptive pain
  - Preclinical promise: morphine-like efficacy
    - Not associated with opioid liabilities, including sedation, respiratory depression, constipation, addiction
  - No currently approved drugs for diabetic neuropathic pain
- Technology/innovation
  - Novel mechanism: NNR
- Time to market
  - Launch 4Q/2004
- Business franchise strength: Emerging
  - Strength in hospital channel (HPD)
  - Strength in neurology (neuropathic pain)
  - Leverage community strength

Revised 05/04/2004 1:14 PM ed... for final presentation/SCM - 01/0004

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Strategic Summary

## ABT-594

◆ **Potential Issues / Threats / Negatives**

- Tolerability issues
  - Nausea, vomiting, dizziness
- Manufacturing/cost of goods
  - Potent Drug
- Efficacy
  - Therapeutic index
- Clinical recruitment
  - Neuropathic pain: evolving clinical research environment
  - Nociceptive pain: mature clinical research environment
- Regulatory risk
  - Neuropathic pain
    - Lack of precedent is threat (more difficult) and opportunity (first mover)
    - Large unmet need may facilitate

Revised 02/14/2008 1:14 PM ahl ... last presentation/BCM - 02/20/08

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Strategic Summary

## ABT-594

◆ **Key Decisions**

**ANNUAL TOTAL COSTS (\$MM)**

2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
9.4	5.6	59.6	55.7	21.8	11.5

Go/No Go  
6/2001

US/EMEA  
Filing  
9/2003

Japan Filing  
9/2004

US/EMEA  
Launch  
9/2004

Revised 02/14/2008 1:14 PM ahl ... last presentation/BCM - 02/20/08

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Strategic Summary

**ABT-594**

**◆ Proposed Action Plans**

**Strategic Analyses**

- Overall pain strategy
  - Abbott
  - Mechanistic and therapeutic diversity and depth to achieve success
  - Currently available assets, including ABT-594
- ABT-594 and NNRs for pain
  - Separation of adverse events and efficacy
    - Pharmaceuticals
    - Titration
    - Pharmacological
  - Oral absorption kinetics
    - Basis of prolonged  $T_{max}$
    - Means to improve (shorten)  $T_{max}$
    - Implications of shortened  $T_{max}$
  - Go/No Go ABT-594
    - 6/2001

Revised 05/14/2001 1:10 PM JAL... in final presentation/02/14 - 05/14/01

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## Abbott Portfolio Review

March 7-9, 2001

- 
- Project: NNR
  - Compound: ABT-594
  - Presenter: Bruce McCarthy, MD

Revised 05/15/2001 1:14 PM ahl . at: hahl presentation@GCM - 10/0201

## ABT-594 Project Team Members

- ◆ Venture Bruce McCarthy, Michael Biarnesen, Marilyn Collicott, Aldona Matalonis, Alyssa O'Neill
- ◆ Statistics David Morris, James Thomas, Yiming Zhang
- ◆ Commercial Laura Robinson, Lisa Lux
- ◆ Pharmacokinetics Walid Awni, Sandeep Dutta
- ◆ Discovery Mike Meyer, Jim Sullivan
- ◆ PARD Howard Cheskin, Lloyd Dias, David Stroz
- ◆ SPD Jim Ciullo
- ◆ Metabolism Joe Machinist, Stan Roberts
- ◆ Toxicology Bill Bracken, Julia Hui
- ◆ Regulatory Jim Steck, David Ross, Nigel Livesey

Revised 05/15/2001 1:14 PM ahl . at: hahl presentation@GCM - 10/0201

### ABT-594 Target Indication

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

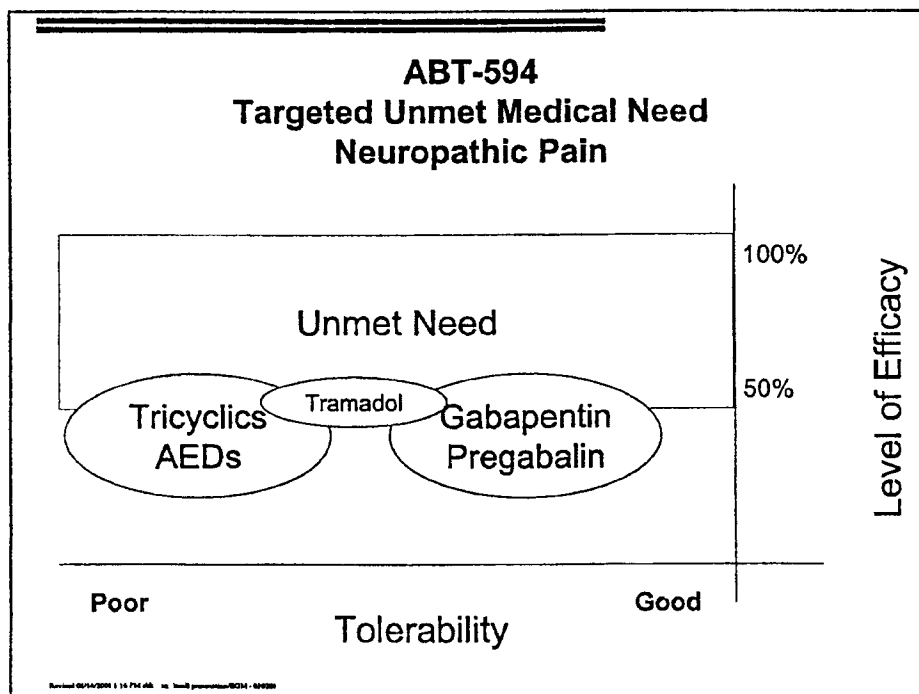
**Upside Claims**

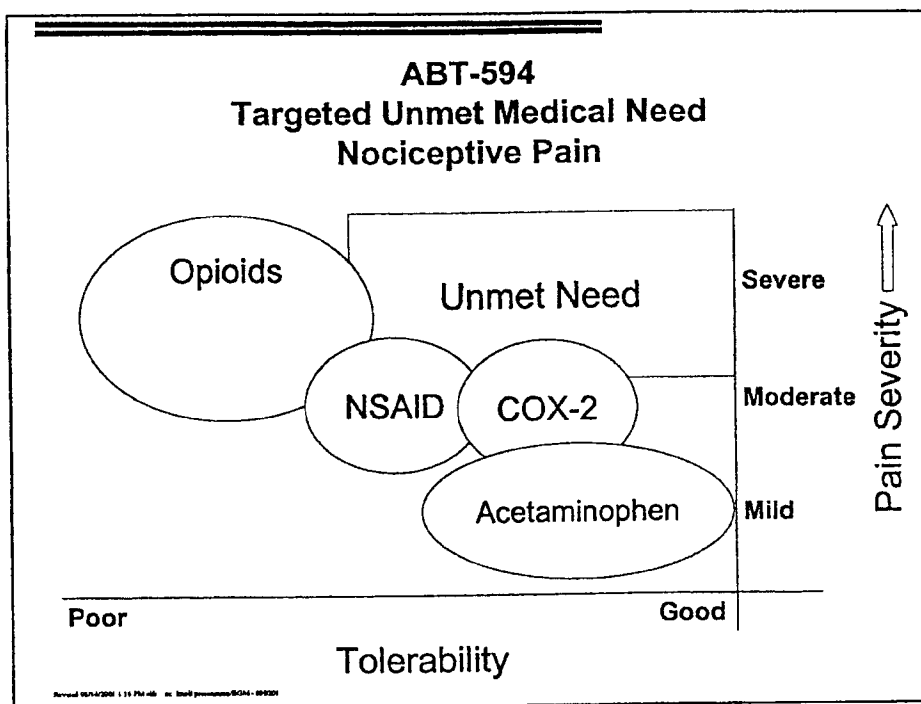
- ◆ Neuropathic Pain
- ◆ Post herpetic neuralgia
- ◆ OA Pain
- ◆ Chronic Pain
- ◆ Cancer Pain

**General Pain Claim**

- ◆ Not viable due to 1.5 hour onset

Revised 05/14/2004 1:14 PM abt vs. Inco's presentation/BDH - 016201





**ABT-594**  
**Targeted Product Profile**

	ABT-594 TARGET PROFILE	Current Gold Standard Gabapentin (Neurontin)
Efficacy	> 40% Average Pain Reduction	39% Average Pain Reduction
Side Effects	< 20% Nausea, Vomiting, Dizziness (during titration)	Somnolence: 23% Dizziness: 24% Confusion: 8% Nausea: 8%
Dosing	BID	TID
Other		Not Labeled for Pain

Revised 10/14/2006 1:16 PM -05 by: David Grossman/SGM - 090201

## ABT-594

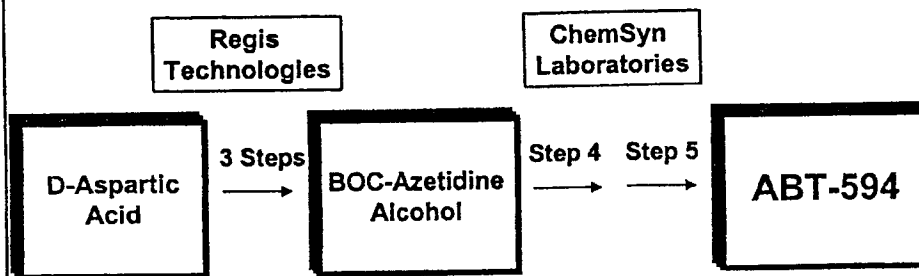
### ◆ Key pre-clinical findings:

- Pharmacology
  - Effective across preclinical models of acute, persistent and neuropathic pain
  - Retains efficacy upon repeated dosing
  - Analgesia via activation of neuronal nicotinic receptors (NNRs) and not via opioid receptors
  - Morphine-like side effects unexpected
    - Constipation
    - Respiratory depression
    - Sedation
- PK/metabolism in animals
  - No CYP interaction
  - No significant metabolism
- Toxicology
  - No issues identified

Revised 06/14/2001 1:18 PM:ab -cc: health protection/SCM - 000301

## ABT-594

### ◆ Chemistry and Manufacturing: Drug Substance (Ebanicline Tosylate)



Commercial Cost Estimate: \$20,000 / Kg Tosylate Salt  
(\$40,000 / Kg Base Equivalent)

Revised 06/14/2001 1:18 PM:ab -cc: health protection/SCM - 000301

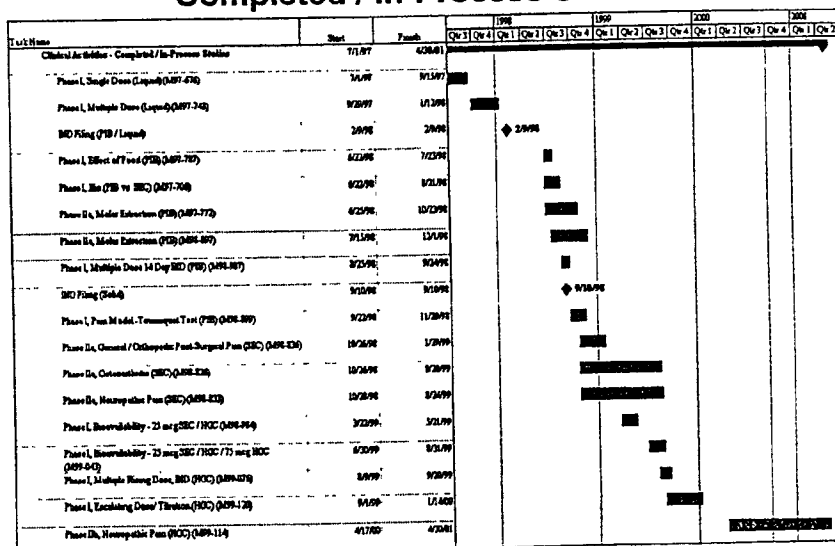
## ABT-594

### ◆ Chemistry and Manufacturing: Drug Product

- Hard Gelatin Capsules
- Dosage strengths: 75, 150, (25)  $\mu$ g Base eq.
- Site: Abbott Puerto Rico
- Manufacturing process:
  - Drug is dissolved in hydro-alcoholic solution
  - Solution sprayed onto micro-porous excipient in a high-shear mixer
  - Granulation is dried, blended with excipients and encapsulated into hard gelatin capsules

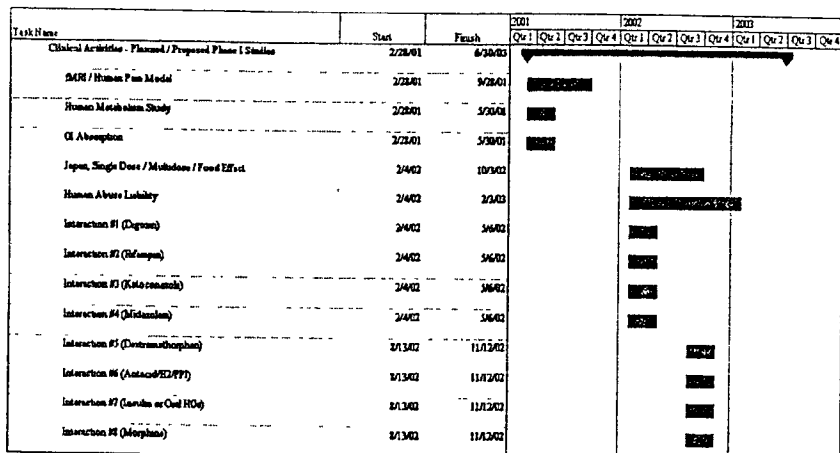
Revised 05/14/2008 1:11 PM ahs - uc final presentation/PCM - 05/20/08

## ABT-594 Global Clinical Development Plan Completed / In-Process Studies



Revised 05/14/2008 1:14 PM ahs - uc final presentation/PCM - 05/20/08

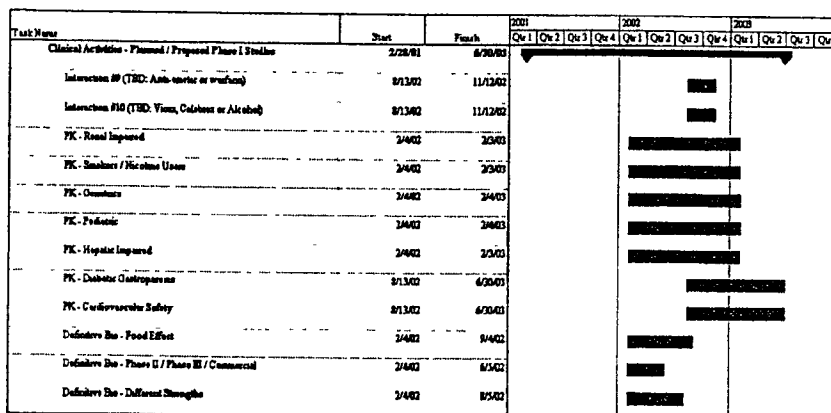
## ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies, Gantt 1 of 2



Revised 06/14/2001 1:14 PM dls. by: [unclear] presentation/BCM - 000001

11

## ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies, Gantt 2 of 2



Revised 06/14/2001 1:14 PM dls. by: [unclear] presentation/BCM - 000001

12



## ABT-594 Global Clinical Development Plan Planned & Proposed Phase II, III & IV Studies

[illegible]

Received 20/04/2004; accepted 15 July 2004; first published online 2004; doi:10.1111/j.1365-2231.2004.00270.x

## ABT-594 Development Budget

(\$MM)	2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
Base Program						
CMC						
- PARD	1.1	2.8	6.2	5.2	3.2	1.0
- SPD	0.1	1.0	1.0	1.0	1.0	1.0
Drug Safety	1.4	0.9	2.3	1.7	0.9	0.5
Other:	1.2	0.5	1.2	-	-	-
Base Program Total	3.8	5.2	10.7	7.9	5.1	2.5
Clinical Program						
Venture Management	4.0	0.2	6.6	6.6	6.0	5.0
Data Mgmt / Stats	0.5	0.2	5.5	7.5	4.7	2.0
Clinical Grants	1.1	0	36.8	33.7	6.0	2.0
Clinical Program Total	5.6	0.4	48.9	47.8	16.7	9.0
Annual Total Costs	9.4	5.6	59.6	55.7	21.8	11.5

Received 25/11/2009; accepted 14/01/2010; published online 20/01/2010

## ABT-594

### ◆ Summary of Phase I findings

- Half-life ( $t_{1/2}$ ): 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{max}$  similar with/without food
- $T_{max}$  may vary somewhat with formulation, food
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

Revised 05/14/2008 1:14 PM v08.00 - final presentation/0204 - 06/08/08

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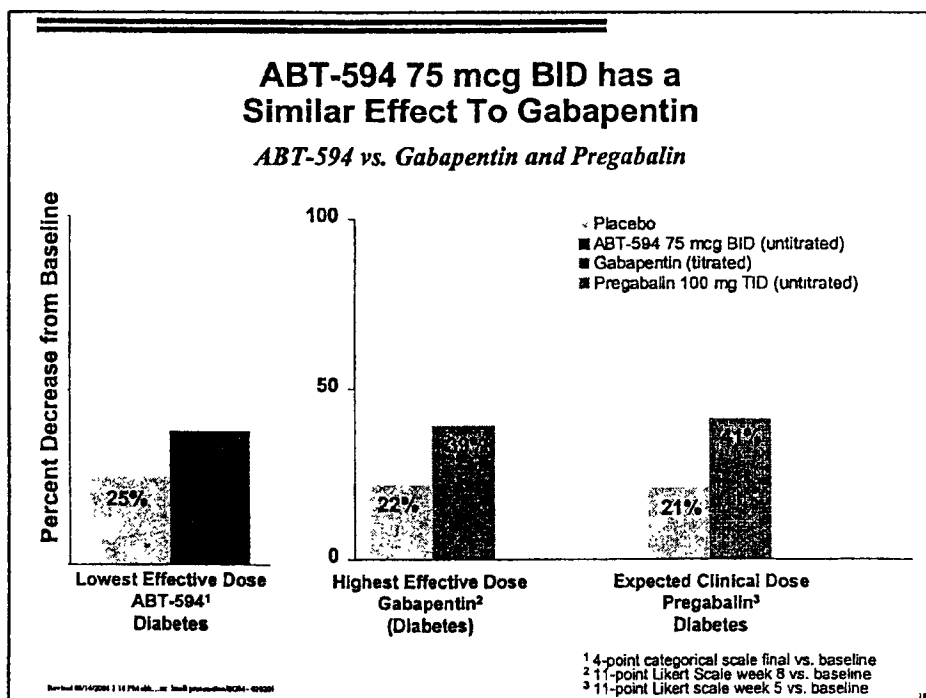
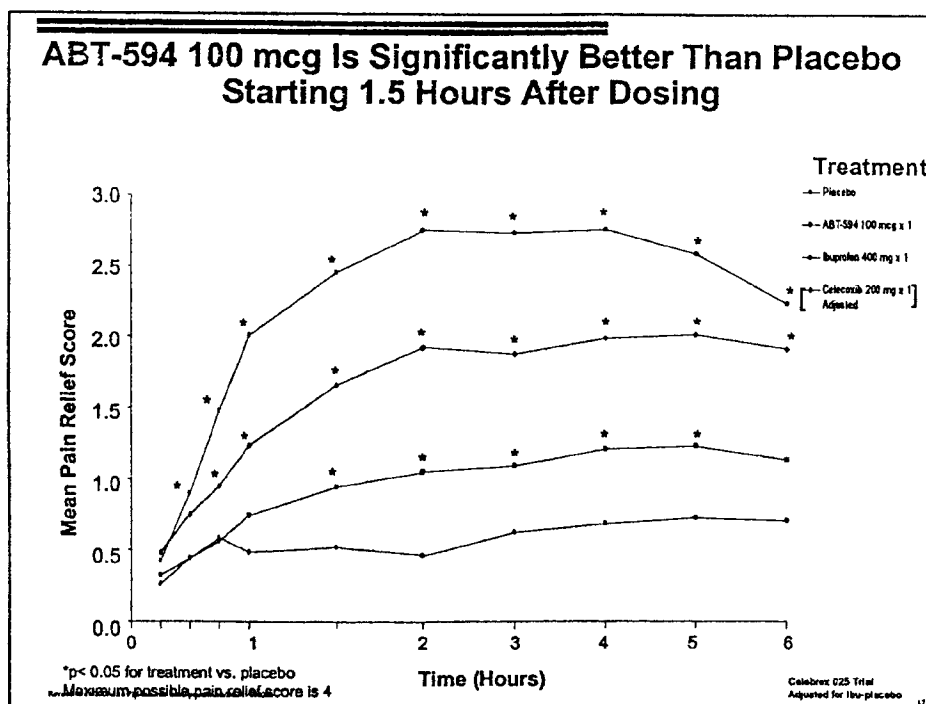
## ABT-594

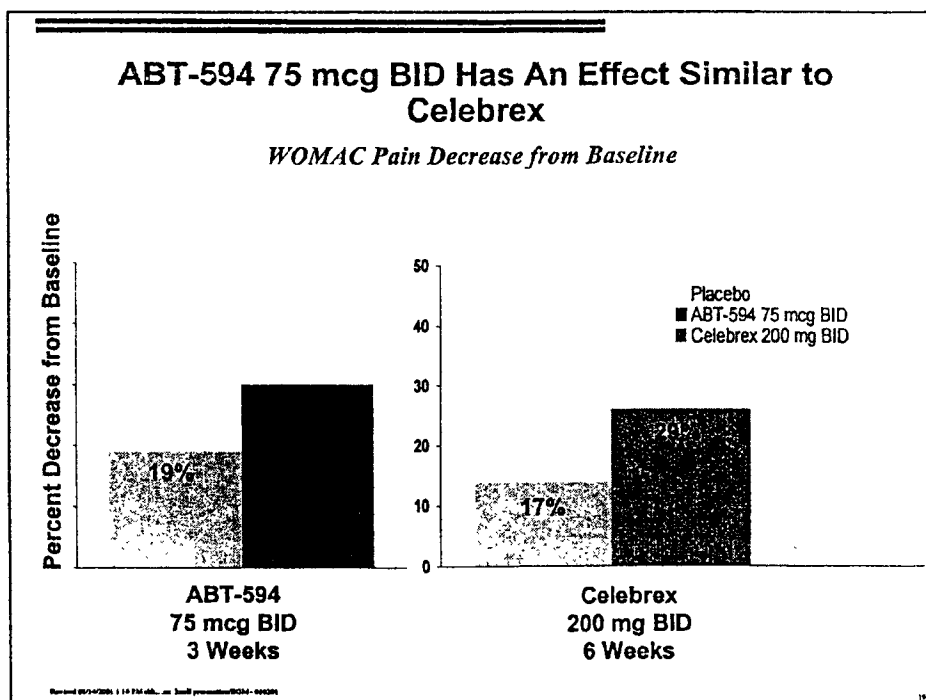
### ◆ Summary of Phase IIa findings

- ABT-594's analgesic potential demonstrated in:
  - Molar Extraction
  - Neuropathic Pain
  - Osteoarthritis
- Well tolerated in chronic Phase IIa studies
  - 75 mcg BID maximum dose
- Limited additional Phase I data suggested re-evaluation of efficacy at higher doses

Revised 05/14/2008 1:14 PM v08.00 - final presentation/0204 - 06/08/08

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**Adverse Event Rates for ABT-594 and Select Analgesics**

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

<sup>1</sup> Max, 1987 (n=29)  
<sup>2</sup> M98-826 and M98-833 combined  
 N/A - Not Available

Revised 05/14/2004 1:14 PM ddb... on Small presentation/ROM - 040204

### Adverse Event Rates for ABT-594 and Select Analgesics

Event	Ultram <sup>1</sup> 50-100 mg q4-6h	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12h	ABT-594 <sup>3</sup> 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

<sup>3</sup> M98-826 and M98-833 combined

N/A - Not Available

Revised 05/04/2001 1:14 PM ab... for final presentation/02/04 - 04/04

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### ABT-594

#### ◆ Summary of Phase IIb Plans

- Neuropathic Pain
  - Improved study design
  - 150, 225, 300 mcg BID
  - Data available 5/2001
- Osteoarthritis
  - Blue plan
- Tolerability evaluation
  - Rate of rise impact
  - Titration

Revised 05/04/2001 1:14 PM ab... for final presentation/02/04 - 04/04

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## ABT-594

### ◆ Regulatory status:

- USA, Canada
  - IND 56,980, solid oral dosage form - Division of Anesthetic, Critical Care, and Addiction Drug Products (1998)
  - IND 55,293, oral solution - Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (1998)
  - Informal Teleconference with FDA, August 26, 1998 (incl. John Hyde, MD)
  - End of Phase II meeting planned, October 2000
- Europe
  - Phase I studies conducted, no regulatory interactions
  - End of Phase II meeting planned, October 2001
- Japan
  - No activity

Revised 05/14/2004 1:14 PM v05...or: final presentation/004 - 00000

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## Strategic Summary

## ABT-594

### ◆ Key Project Strengths / Positives

- Product attributes
  - Orally available
  - May be effective for neuropathic and nociceptive pain
  - Preclinical promise: morphine-like efficacy
    - Not associated with opioid liabilities, including sedation, respiratory depression, constipation, addiction
  - No currently approved drugs for diabetic neuropathic pain
- Technology/innovation
  - Novel mechanism: NNR
- Time to market
  - Launch 4Q/2004
- Business franchise strength: Emerging
  - Strength in hospital channel (HPD)
  - Strength in neurology (neuropathic pain)
  - Leverage community strength

Revised 05/14/2004 1:14 PM v05...or: final presentation/004 - 00000

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**Strategic Summary**

## ABT-594

◆ **Potential Issues / Threats / Negatives**

- Tolerability issues
  - Nausea, vomiting, dizziness
- Manufacturing/cost of goods
  - Potent Drug
- Efficacy
  - Therapeutic index
- Clinical recruitment
  - Neuropathic pain: evolving clinical research environment
  - Nociceptive pain: mature clinical research environment
- Regulatory risk
  - Neuropathic pain
    - Lack of precedent is threat (more difficult) and opportunity (first mover)
    - Large unmet need may facilitate

Revised 05/14/2001 1:10 PM AB... m: final presentation/SCM - 03/02/01

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**Strategic Summary**

## ABT-594

◆ **Key Decisions**

**ANNUAL TOTAL COSTS (\$MM)**

2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
9.4	5.6	59.6	55.7	21.8	11.5

Go/No Go  
6/2001

US/EMEA  
Filing  
9/2003

Japan Filing  
9/2004

US/EMEA  
Launch  
9/2004

Revised 05/14/2001 1:10 PM AB... m: final presentation/SCM - 03/02/01

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Strategic Summary

## ABT-594

◆ **Proposed Action Plans**

Strategic Analyses

- Overall pain strategy
  - Abbott
  - Mechanistic and therapeutic diversity and depth to achieve success
  - Currently available assets, including ABT-594
- ABT-594 and NNRs for pain
  - Separation of adverse events and efficacy
 

- Pharmaceuticals
    - Titration
    - Pharmacological

$\left. \vphantom{\begin{matrix} - Pharmaceuticals \\ - Titration \\ - Pharmacological \end{matrix}} \right\} \begin{matrix} \text{ABT-594} \\ \text{Follow-ons} \end{matrix}$
  - Oral absorption kinetics
    - Basis of prolonged  $T_{\max}$
    - Means to improve (shorten)  $T_{\max}$
    - Implications of shortened  $T_{\max}$
  - Go/No Go ABT-594
    - 6/2001

Revised 10/14/2001 1:16 PM JAB, inc. health presentation/0014 - 05A200

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**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Wednesday, March 7**

7:30 am	Welcome/ introduction	10 min		J. Leiden
7:40 am	Meeting objectives	10 min		J. Leonard
	<b>Anti-Infectives</b>	<b>Presentation</b>	<b>Discussion</b>	
	Quinolones			
7:50 am	- ABT- 492	20 min	5 min	C. Craft
8:15 am	- HSR- 903	30 min	10 min	T. Hirose/R. Krautheimer
	<b>Anti-virals</b>			
8:55 am	Triangle projects	30 min	10 min	M. Heath-Chiozzi
	- HIV and HBV (FTC; DAPD)			
9:35 am	<b>Morning Break</b>			
	<b>Urology</b>			
9:55 am	BSF 420627 (ETA/ BPH)	30 min	10 min	M. Kirchengast
	<b>T3/T4</b>			
10:35 am	T3/T4	15 min	5 min	C. Schreiber/T. Miller
	<b>Asthma</b>			
10:55 am	Hokunalin tape	15 min	5 min	T. Hirose/R. Krautheimer
	<b>Oncology</b>			
11:15 am	ABT-510	20 min	15 min	P. Nisen
11:50 am	ABT-751	20 min	15 min	P. Nisen
12:25 pm	<b>Lunch</b>			
1:25 pm	ABT-518	15 min	5 min	P. Nisen
1:45 pm	Rubitecan	20 min	5 min	P. Nisen
2:10 pm	Theragyn	20 min	5 min	P. Nisen
2:35 pm	ABT-627	30 min	10 min	P. Nisen
3:15 pm	<b>Afternoon Break</b>			
	<b>Cardiology</b>			
3:35 pm	Darusentan	45 min	10 min	M. Luz/M. Kirchengast
	(LU 135252)			
	LU208075			M. Luz/M. Kirchengast
	<b>Thrombosis</b>			
4:30 pm	PEG-hirudin	30 min	10 min	V. Ifthekar/U. Legler
5:10 pm	Ancrod	30 min	10 min	D. Levy/U. Legler
5:50 pm	Urokinase/ Pro-urokinase	30 min	10 min	S. Guptha

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Thursday, March 8**

<b>Neuroscience</b>		<b>Presentation</b>	<b>Discussion</b>	
7:30 am	ABT 594	30 min	10 min	B. McCarthy
8:10 am	ABT-963	15 min	15 min	Granneman/Doan/Bell
8:40 am	BSF 201640	30 min	10 min	B. Rendenbach-Mueller
9:20 am	BSF 74398 (Parkinson)	30 min	10 min	S. Dawe
10:00 am	<b>Morning Break</b>			
10:20 am	Dilaudid OROS	45 min	15 min	B. Gold/R. Krautheimer
11:20 am	BSF 190555 (Schizophrenia)	30 min	10 min	B. Rendenbach-Mueller
12:00 pm	<b>Lunch</b>			
1:00 pm	Hydrocodone	10 min	10 min	S. Collins
1:20 pm	Bimoclomol ( ABT-822)	30 min	10 min	B. Wallin
	<b>Gastro-enterology</b>			
2:00 pm	Ganaton (pro-kinetic)	15 min	5 min	S. Dawe/R. Krautheimer
2:20 pm	TU-199 (proton pump inh.)	30 min	10 min	T. Hirose/ R. Krautheimer
3:00 pm	AU - 224 (colon pro-kinetic)	20 min	5 min	T. Hirose/ R. Krautheimer
3:25 pm	<b>Afternoon Break</b>			
	<b>Phase III Projects</b>			
3:45 pm	ABT-773	30 min	15 min	C. Craft
4:30 pm	D2E7	45 min	30 min	C. Spiegler/E. v. Borcke

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Friday, March 9**

**Phase III Projects (cont'd)**

		<b>Presentation</b>	<b>Discussion</b>	
7:30 am	Segard	45 min	15 min	L. Daum/T. King
8:30 am	J695	30 min	10 min	R. Janocha/T. King
9:10 am	Clivarine	30 min	15 min	F. Misselwitz/S. Schaeffer
9:55 am	<b>Morning Break</b>			
10:15 am	Rythmol SR	30 min	15 min	A. Pethö-Schramm/E. Schneider
11:00 am	Levosimendan	30 min	15 min	C MacLeod

**Phase IV Projects**

11:45 am	Clarithromycin	15 min	5 min	C. Olson
12:05 pm	Omnicef	15 min	5 min	C. Olson
12:25 pm	<b>Lunch</b>			
1:25 pm	Kaletra	15 min	5 min	E. Sun
1:45 pm	Norvir	15 min	5 min	E. Sun
2:05 pm	Meridia ( Sibutramine )	15 min	5 min	E. Chong/W. Hargan
2:25 pm	Uprima	15 min	5 min	S. Bukofzer
2:45 pm	Trandolapril (patch, intervention trials)	15 min	5 min	B. Rendbach-Mueller/ U. Legler/N. Bender
3:05 pm	<b>Afternoon Break</b>			
3:25 pm	Fenofibrate	15 min	5 min	D. Yannicelli
3:45 pm	Depakote	15 min	5 min	K. Sommerville
4:05 pm	Gengraf	15 min	5 min	T. Japour
4:25 pm	<b>Conclusion</b>			Jeff Leiden



# **ABT-773 Update March 19, 2001**

## **Agenda**

- **Market and trends**
- **Molecule**
- **Microbiology**
- **Pharm/tox**
  - **QT prolongation**
  - **Hepatotoxicity**
- **Clinical development**
  - **Phase I/II summary**
  - **Dose selection**
  - **Phase III program**
  - **Contingency plans**
- **Timeline and budget**
- **IV formulation**
- **Summary of key issues and action plans**

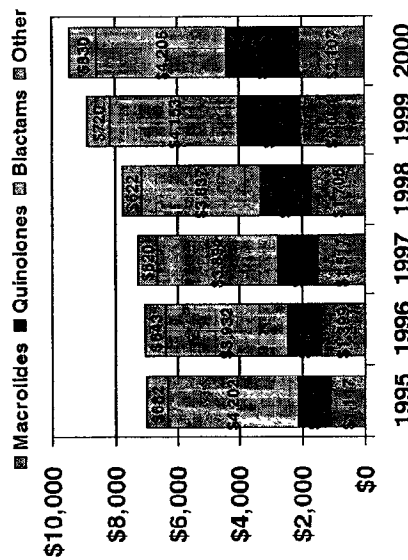
## Market and Drivers

- Infectious disease accounts for 13.3 million deaths yearly worldwide, 25% of all deaths
- Antibiotics are the 2<sup>nd</sup> most commonly prescribed category of drugs
- The global antibiotic market is a \$21B market, the 5<sup>th</sup> largest global market in sales
- The global antibiotic market has shown modest sales growth
  - 3.9% CAGR<sub>96-00</sub> in sales for overall combined market
  - 4.7% CAGR<sub>96-00</sub> in sales for branded combined market
- Sales growth in the U.S. has been driven by replacement of older generic agents with newer branded agents (most other markets show increasing generic use)
  - Antibiotic resistance results in OBSOLESCENCE of existing agents over time (a CHRONIC problem)
  - Sales per TRX rose from \$18.42 in 1995 to \$28.05 in 2000 (8.8% CAGR)
  - Generics still represent 61% of TRX, representing an opportunity for conversion
- Generics have been more stable ex-U.S

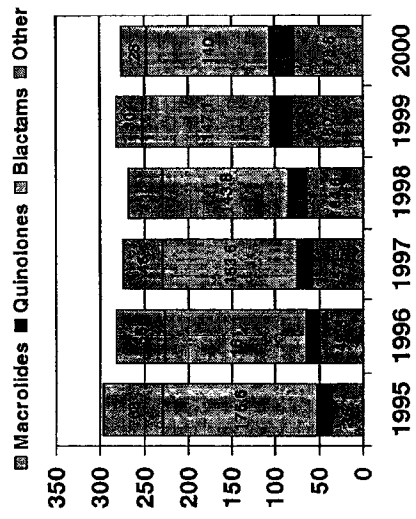


# U.S. Market Trends

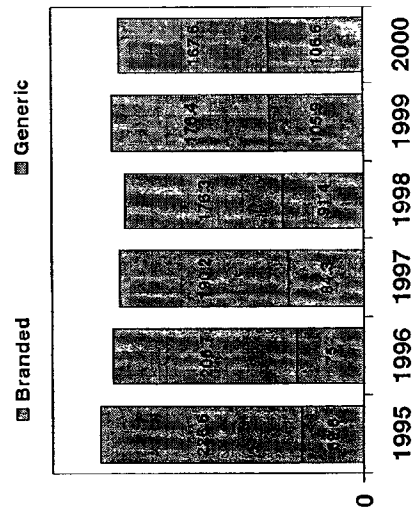
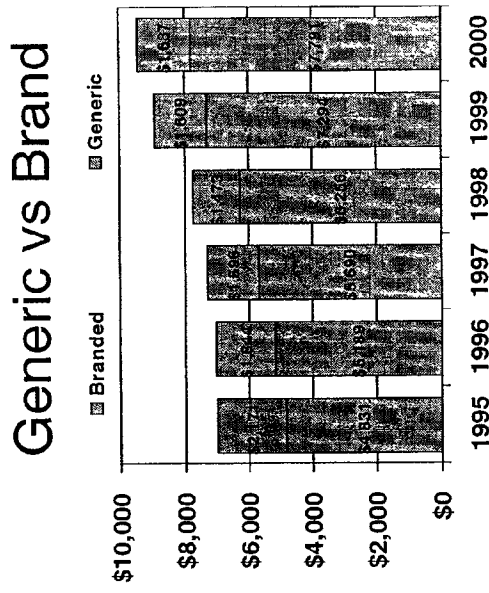
## By Class



**SALES**  
CAGR<sub>95-99</sub>: 6.1%  
10.0% Branded  
-5.5% Generic



**TRX (excludes IV)**  
CAGR<sub>95-99</sub>: -1.5%  
8.9% Branded  
-5.9% Generic



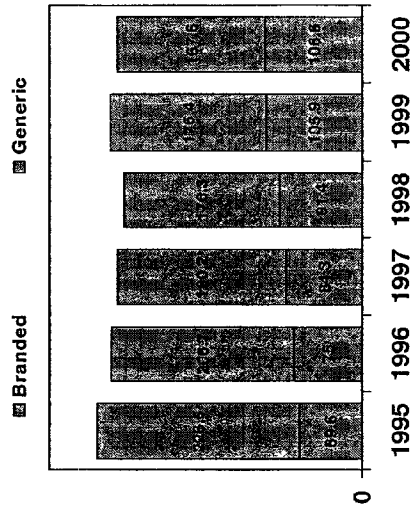
Macrolides and quinolones have driven the growth of the market

Generic use decreasing with increasing antibiotic resistance

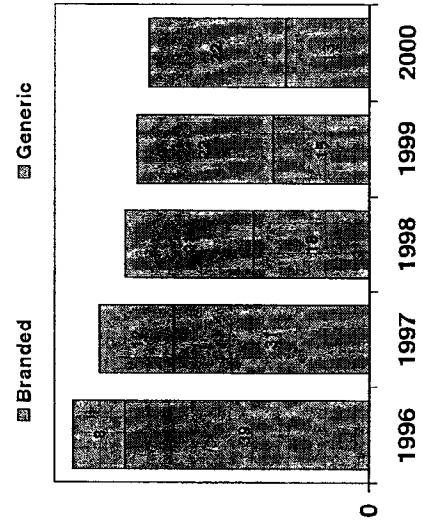
While most markets tend toward increasing utilization of generics, the antibiotic market is tending toward decreasing utilization of generics-OBSOLESCENCE

## Backup

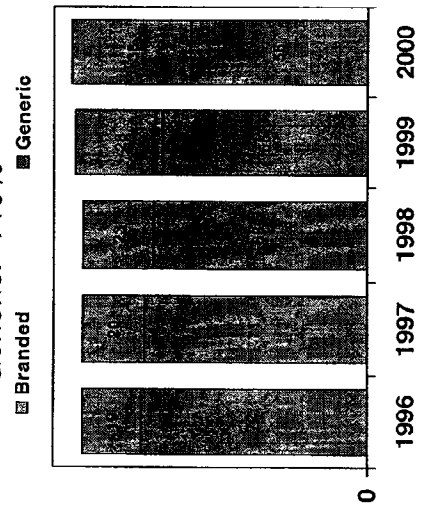
**Antibiotics**  
Brand: +9%  
Generic: -6%



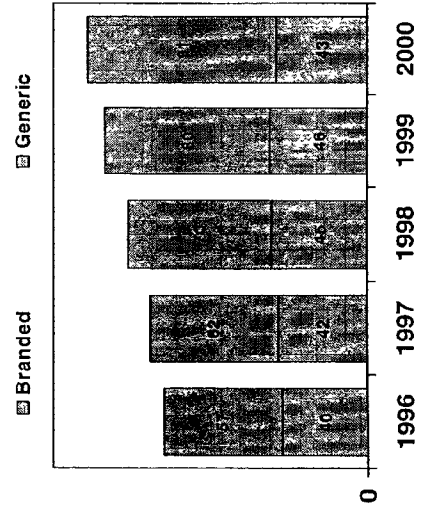
**H2 Antagonists**  
Brand: -25%  
Generic: +29%



**Calcium Blockers**  
Brand: -6%  
Generic: +19%



**Beta Blockers**  
Brand: +2%  
Generic: +13%



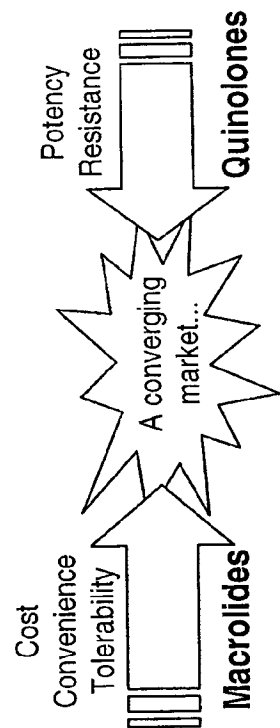
# Antibiotic Classes

3 antibiotic classes dominate the market, representing 89% of global sales

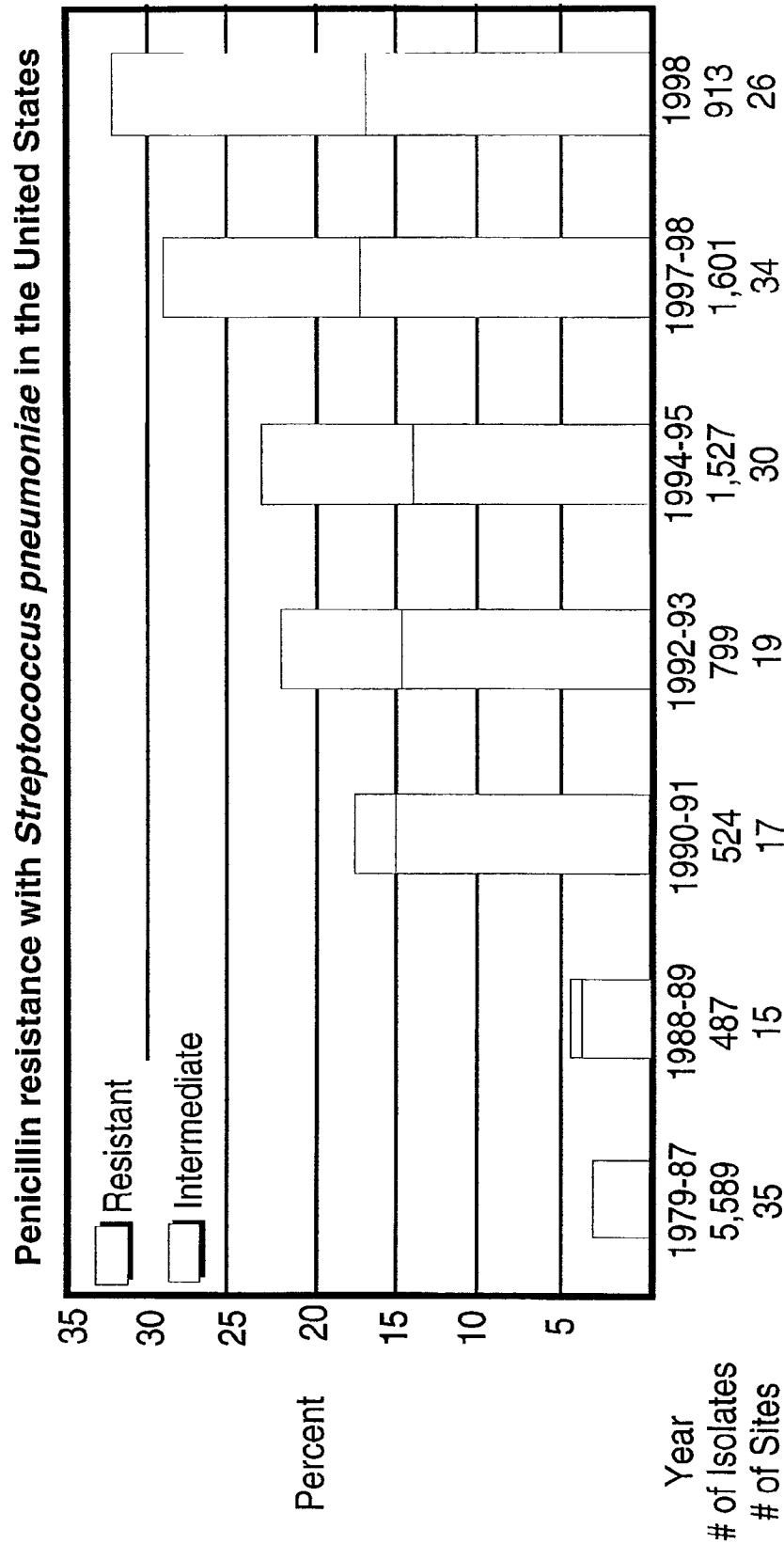
Class Dominant Brand	Other Brands	Global Class Sales (\$MM)	Ped	IV	Comment
B-lactam Augmentin	Ceftin, Cefzil, pens, amox	\$10,561	X	X	<ul style="list-style-type: none"> <li>•B-lactams 1.1% CAGR; -1.4% Y-Y</li> <li>•High generic penetration</li> <li>•Augmentin unique, due to resistance</li> </ul>
Macrolide Zithromax	Biaxin erys	\$4,066	X	X	<ul style="list-style-type: none"> <li>•Macrolides 8.1% CAGR; 2% Y-Y</li> <li>•Zithromax set new standards in cost, convenience, tolerability</li> <li>•Z growth has slowed (5% Y-Y) due to maturing brand and resistance</li> </ul>
Quinolone Levaquin	Cipro Tequin Avelox	\$3,750	Under Dev	X	<ul style="list-style-type: none"> <li>•Quinolones 11% CAGR, 10% Y-Y</li> <li>•Leveraging macrolide resistance to become fastest growing class</li> <li>•New quinolones have overcome narrow spectrum and poor tolerability</li> </ul>

CAGR = Global 1995-2000 compound annual growth rate

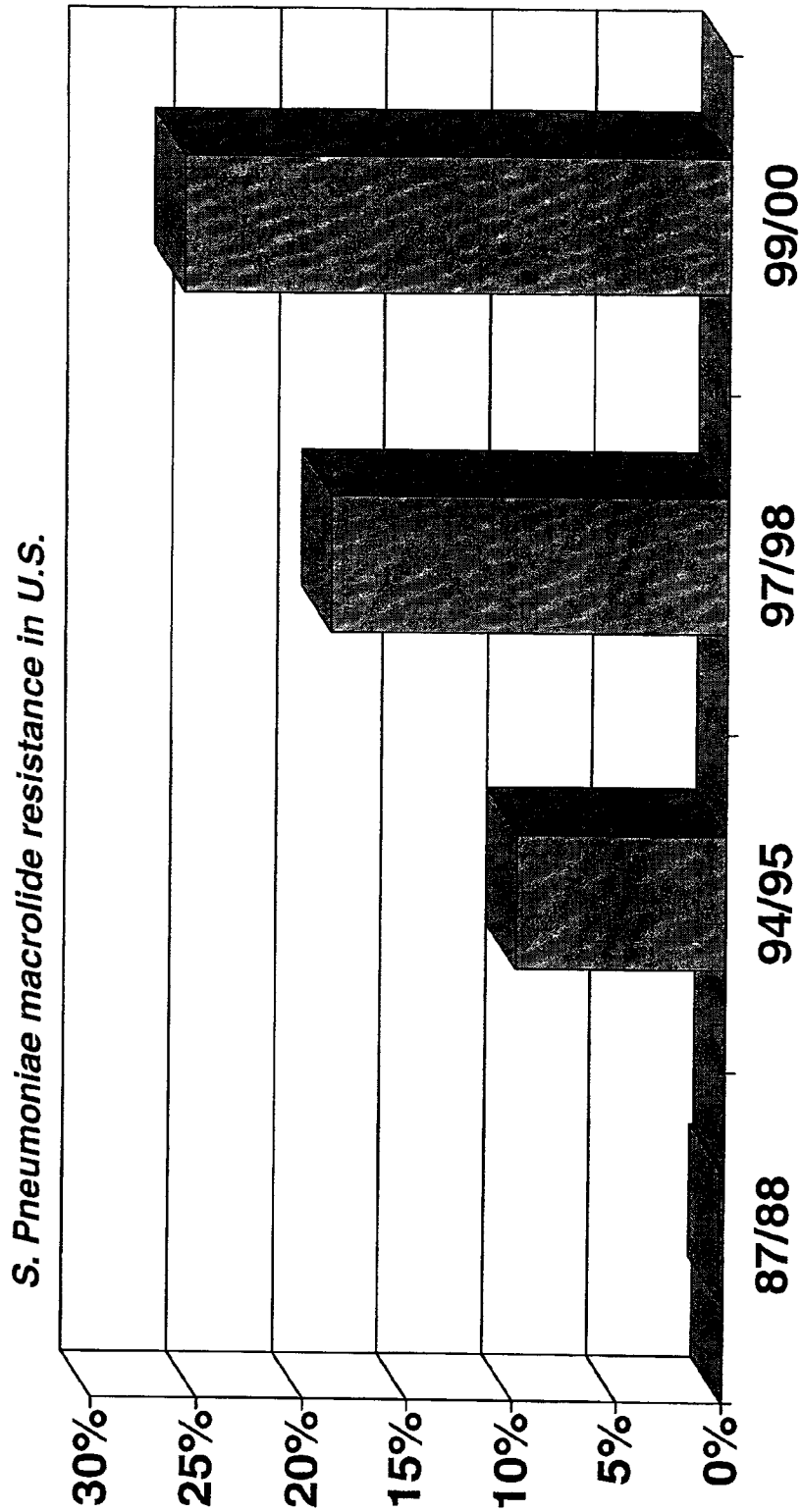
- Macrolides expanded the market on the basis of Pen/B-lactamase resistance, cost, convenience, and tolerability
- Quinolones (+11% CAGR) are now driving the market from a macrolide resistance standpoint (while near parity on cost, convenience, tolerability)



**Biaxin and Zithromax were able to leverage increasing Pen resistance to create a compelling selling proposition**



**Quinolones are now leveraging macrolide resistance in the same fashion to become the fastest growing class**



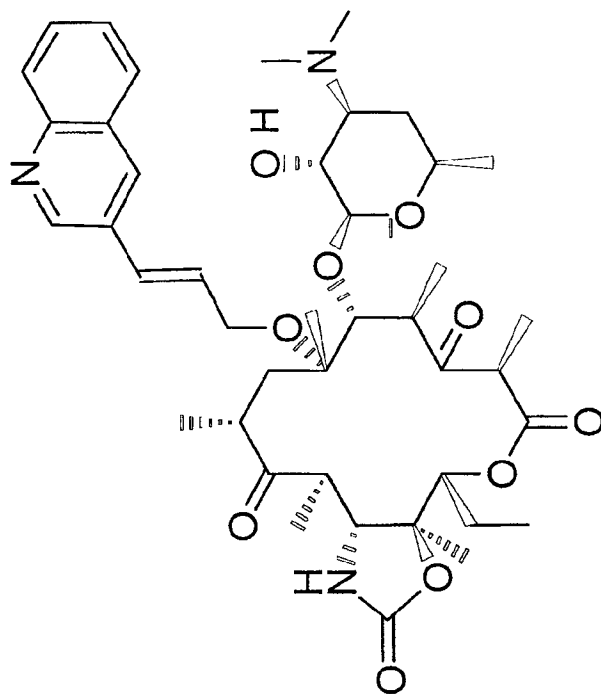
# ABT-773 Target Profile

	ABT-773	Levaquin	Zithromax
Convenience	Target is QD dosing all indications Potential for BID in CAP & sinusitis  Duration: 5d, 10 d (parity to Zithromax) <b>PARITY IF QD</b>	All RTI regimens 500 mg QD, 7-14 d	250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP
Efficacy	Statistically equivalent cure/eradication to comparators; can take advantage of macrolide/penicillin resistance <b>PARITY</b>	Statistically equivalent cure/eradication to comparators; gold standard for CAP with IV; can take advantage of macrolide/penicillin resistance	Statistically equivalent cure/eradication to comparators; availability of IV adds to efficacy image; subject to increasing levels of macrolide resistance
Activity	Most active agent for Gram + pathogens, including telithromycin; parity for atypicals; parity to Zithromax for Gram -, through inferior to quinolones (weakness)	Highly active against most clinically relevant respiratory pathogens; potential issue with increase in Gram - resistance; theories that Gram + quinolone resistance may increase dramatically/rapidly with increased use	Not as active as clari in Gram + pathogens, increasing macrolide resistance, moderate Gram - activity
Adverse Events	Taste perversion: 4% Diarrhea: 10% <b>COMPARABLE TO BIAXIN XL</b>	Very well tolerated and safe	Very well tolerated; GI disturbance ~ 2-5%; no taste perversion
Resistance Claim	Being pursued; important to development of resistance story; availability of IV will increase likelihood of claim	Claim for pen-R Strep. pneumo	None
Price	Parity to Zithromax	\$60 for 7 days	\$43 for 5 days
Other	Attempt to leverage "best of both worlds" message i.e. potency & resistance coverage of a quinolone with safety & appropriateness of macrolide	Some class-related negative perceptions among some physicians with respect to AEs and appropriate use, but with increased use these barriers are eroding	



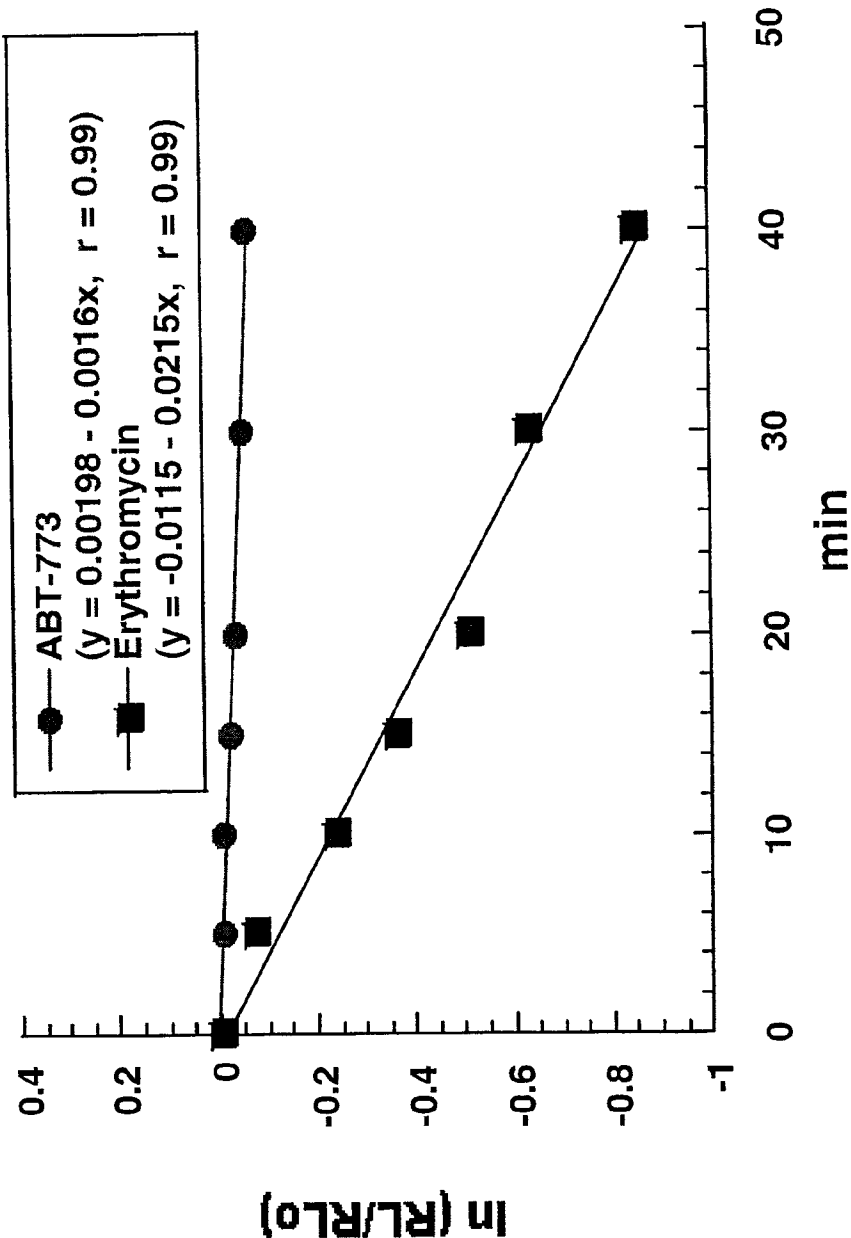
# ABT-773 SAR

- Quinolylallyl propenyl moiety at the 6-O –position (↑ PK, activity)
- Carbamate group at the 11, 12-position (↑ activity vs macrolide-resistant Strep)
- Keto group at the 3-position (confers *erm* non-induction)



- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.



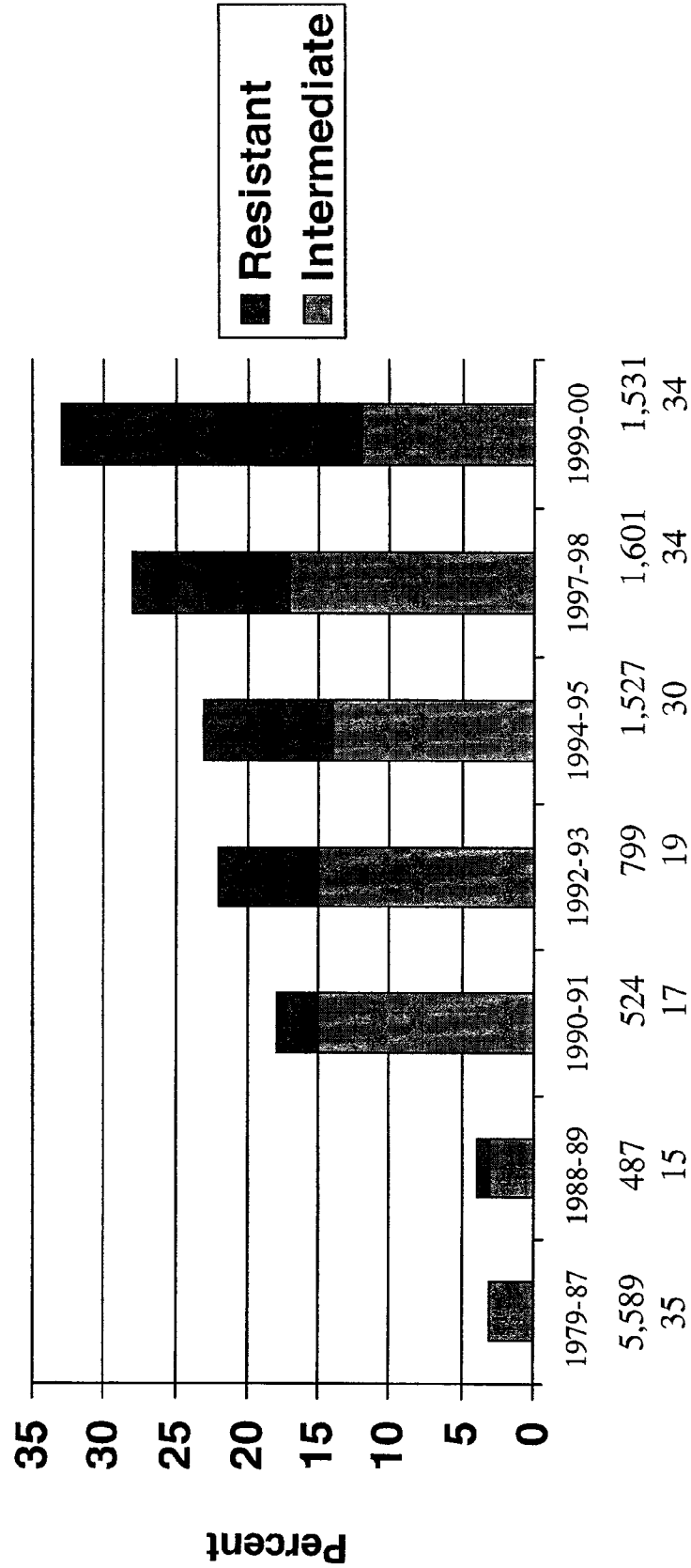
# ABT 773 Microbiology

MIC90	Clari	Trovan*	Ketek	ABT-773
<i>S. Pneumoniae</i> (susc)	< 0.03	0.125	0.008	< 0.002
<i>S. Pneumoniae</i> (mef)	8.0	0.125	1	0.12
<i>S. Pneumoniae</i> (erm)	> 32	0.125	0.12	0.01
<i>S. Pyogenes</i> (mef)	16	0.125	1	0.12
<i>S. Pyogenes</i> (erm)	> 32	0.25	> 8	0.5
<i>M. catarrhalis</i>	0.03	0.015	0.25	0.25
<i>H. influenzae</i>	8	0.015	2	2

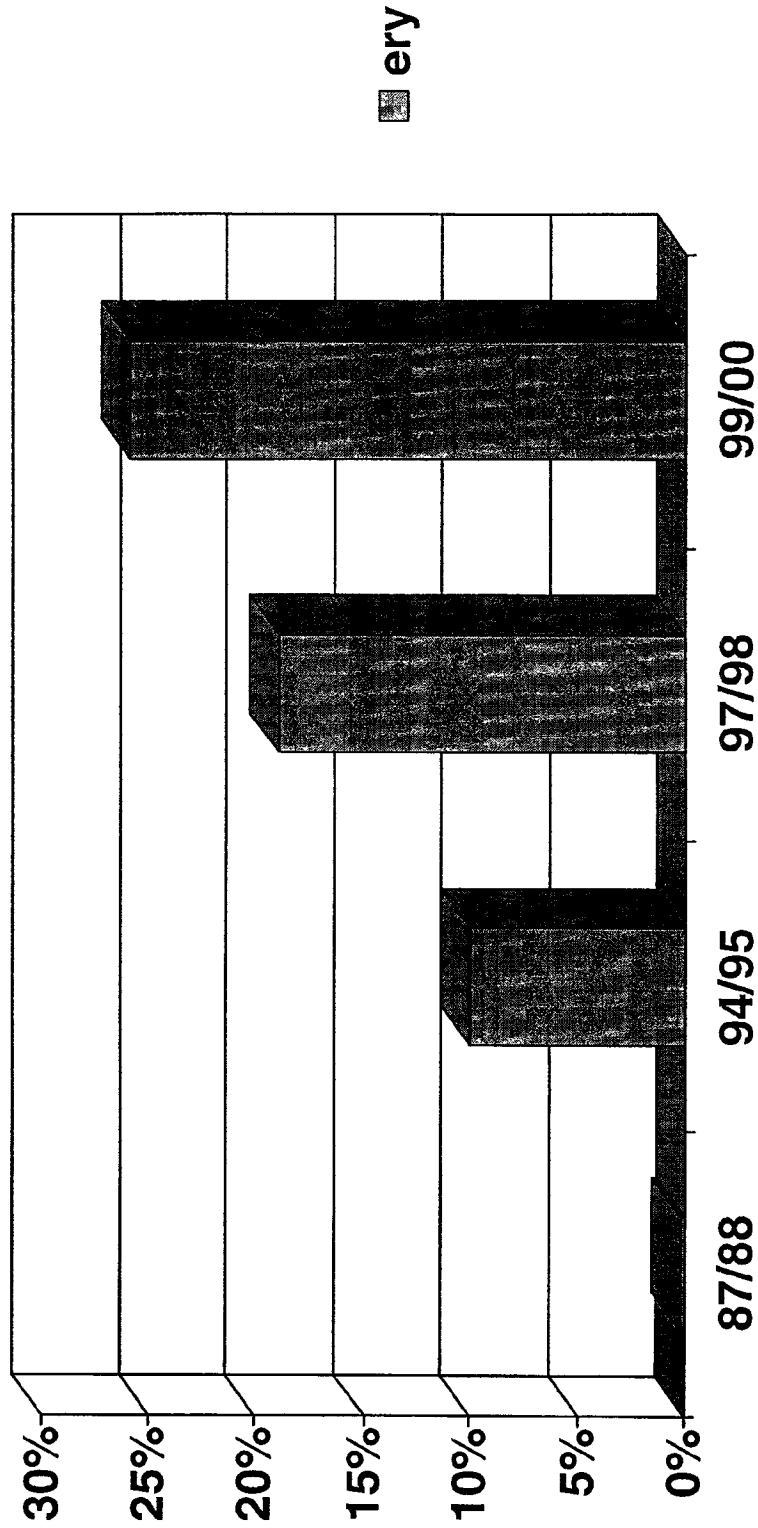
\* Withdrawn from market, but among the more potent quinolones

# Microbiology

## Penicillin resistance with *Streptococcus pneumoniae* in the United States



## *S. pneumoniae* Macrolide Resistance from U.S. Surveillance



US surveillance studies: Doern et al.

# Preclinical/Clinical Issues

- QT prolongation
- Hepatotoxicity

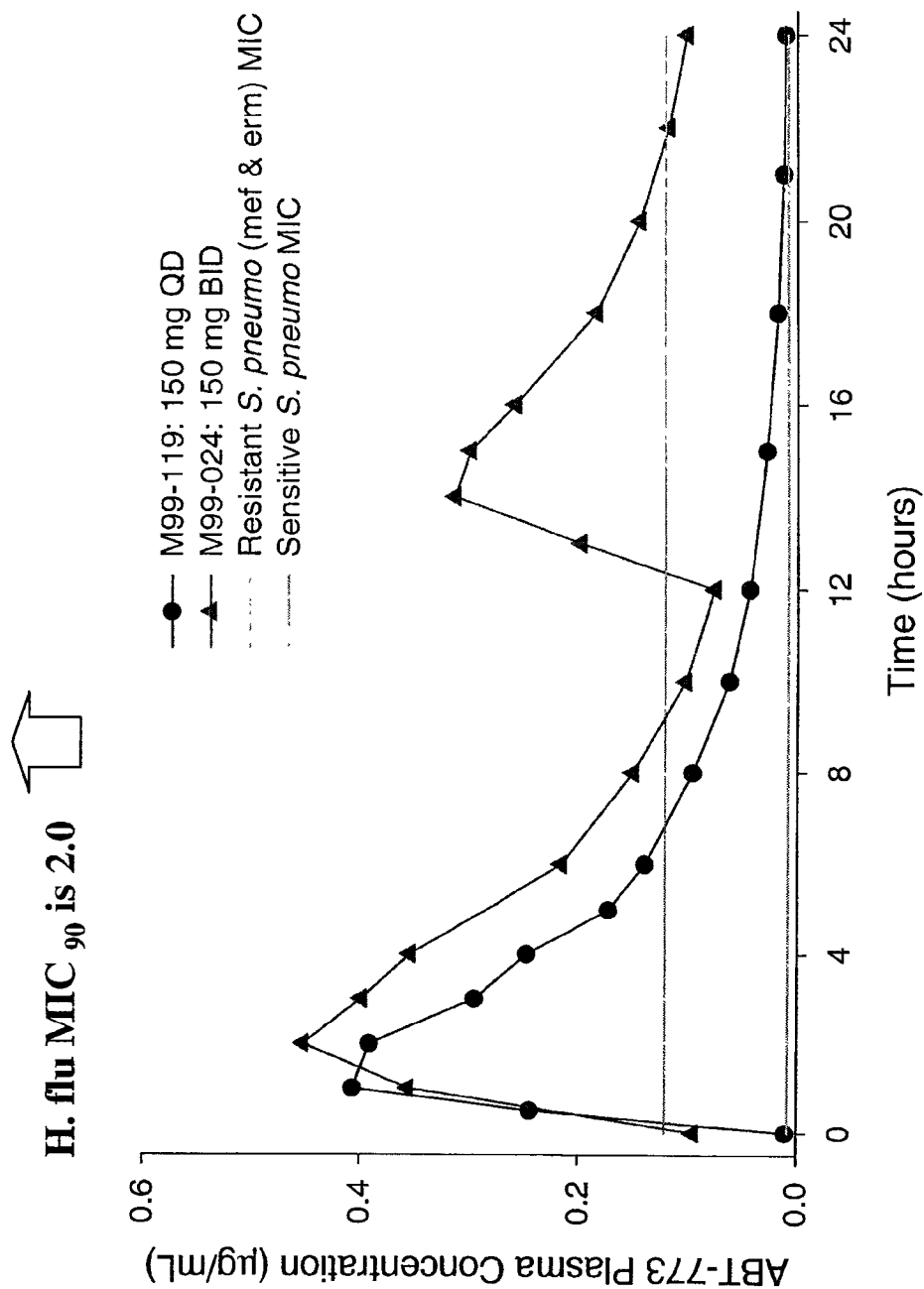
# QT Prolongation

- **Purkinje fiber repolarization**
  - APD increase at 5 mcg/mL (10x clinical Cmax) in the absence of plasma proteins, but not in their presence
  - Moxi > Clari > Ery ~ ABT-773 > Levo (without plasma)
- **Dogs**
  - no significant effect on QTc up to 9 mcg/mL
  - 11% increase (40 msec) at 22 mcg/mL
  - Telemetry-instrumented dog study requested by FDA will be completed by May 1, 2001
- **Humans**
  - Possible dose effect in Phase I at daily dose > 800 mg
  - No significant QT effect in ketoconazole interaction study
  - No clinically relevant QT effect in Phase II studies 150 – 600 mg daily (n=412)

# Hepatotoxicity

- Toxicology studies
  - NTEL for LFT abnormalities in rat = 3-8 x clinical AUC
  - NTEL for LFT abnormalities in monkey = 2-4 x clinical AUC
- Clinical experience
  - No evidence of LFT issue in Western subjects (<1% asx LFT elevation in >1000 pts in phase II-III studies)
  - Japanese in bridging study showed increased LFTs.
    - 7 of 42 (17%) Japanese subjects had >3x ULN
    - No evidence of dose response
    - Repeat study in Japan showed no evidence of LFT increases in Japanese (n=60) or Caucasians (n=8).

# ABT 773 Pharmacokinetics



# Phase II Clinical Studies

Study	Dose/Duration	Number of subjects
ABECB	150, 300 or 600 mg OD Duration: 5 days	N = 384
Acute Sinusitis	150, 300, or 600 mg OD Duration: 10 days	N = 292
CAP	300 or 600 mg OD Duration: 7 days	N = 187



# Phase II Results

## Combined ABECB, CAP, ABS Clinical Response

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
<b>Clin and Bact. Eval</b>	<b>84%</b> (42/50)	<b>90%</b> (103/115)	<b>88%</b> (106/120)
<b>Clin Eval</b>	<b>88%</b> (168/193)	<b>88%</b> (247/279)	<b>81%</b> (216/265)
<b>ITT</b>	<b>83%</b> (176/211)	<b>82%</b> (259/314)	<b>75%</b> (230/305)

# ABT 773 Phase II Findings

## Combined ABECB, CAP, ABS Adverse Events

GI and Taste	<u>150 mg QD</u>			<u>300 mg QD</u>			<u>600 mg QD</u>		
Taste Perversion	4%	(8/223)		17%	(55/322)		27%	(87/318)	
Diarrhea	10%	(22/223)		11%	(34/322)		19%	(60/318)	
Nausea	5%	(12/223)		12%	(40/322)		26%	(83/318)	
Vomiting	2%	(4/223)		6%	(19/322)		14%	(44/318)	

# Phase II: 150 mg QD vs 300 mg QD

Phase IIb Data: Intent-to-treat										
		Bronchitis		CAP		Sinusitis		Total		
Clinical Cure	150 mg QD	85%	104/123			82%	72/88	83%	176/211	
	300 mg QD	83%	107/129	84%	80/95	80%	72/90	82%	159/314	
Bacteriological Cure	<i>H. flu</i>	150 mg QD	89%	17/19			60%	3/5	83%	20/24
		300 mg QD	81%	17/21	100%	9/9	100%	7/7	89%	33/37
	<i>S. pneumo</i>	150 mg QD	77%	10/13			100%	3/3	81%	13/16
		300 mg QD	90%	9/10	82%	14/17	100%	8/8	89%	31/35

# Community-Acquired Pneumonia

## Clinical Response

300 mg                      600 mg

Clin and Bact. Eval	92%    (54/59)	82%    (47/57)
Clin Eval	92%    (72/78)	80%    (56/70)
ITT	84%    (80/95)	73%    (65/89)

## Phase II summary

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD selected for ABECB and pharyngitis in pivotal phase III comparative studies
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

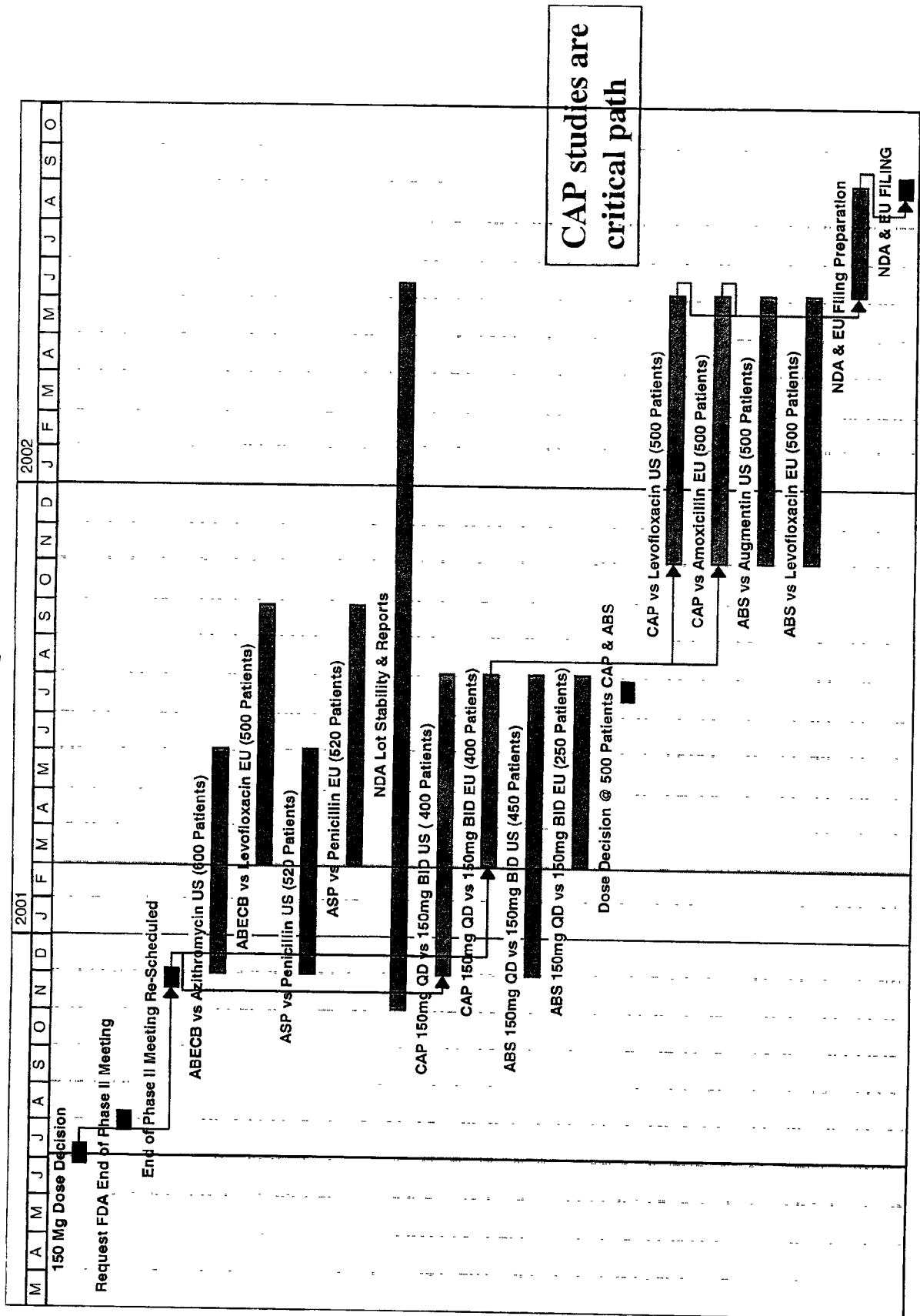
## Dose selection: Divergent U.S. and European regulatory and commercial considerations

- **US**
  - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
  - Approval on indication-by-indication basis
- **Europe**
  - Relatively minor commercial impact of BID dosing
  - CAP indication is critical for overall approval

# ABT 773 Indications

Infection	Dosage	Duration
Pharyngitis/Tonsillitis (ASP)	150 mg QD	5 d
Acute bacterial exacerbation of chronic bronchitis (ABECB)	150 mg QD	5 d
Acute bacterial sinusitis (ABS)	150 mg QD or BID	10 d
Community-acquired pneumonia (CAP)	150 mg QD or BID	10 d

# ABT 773 Development Timeline





## Phase III: ABECB and ASP

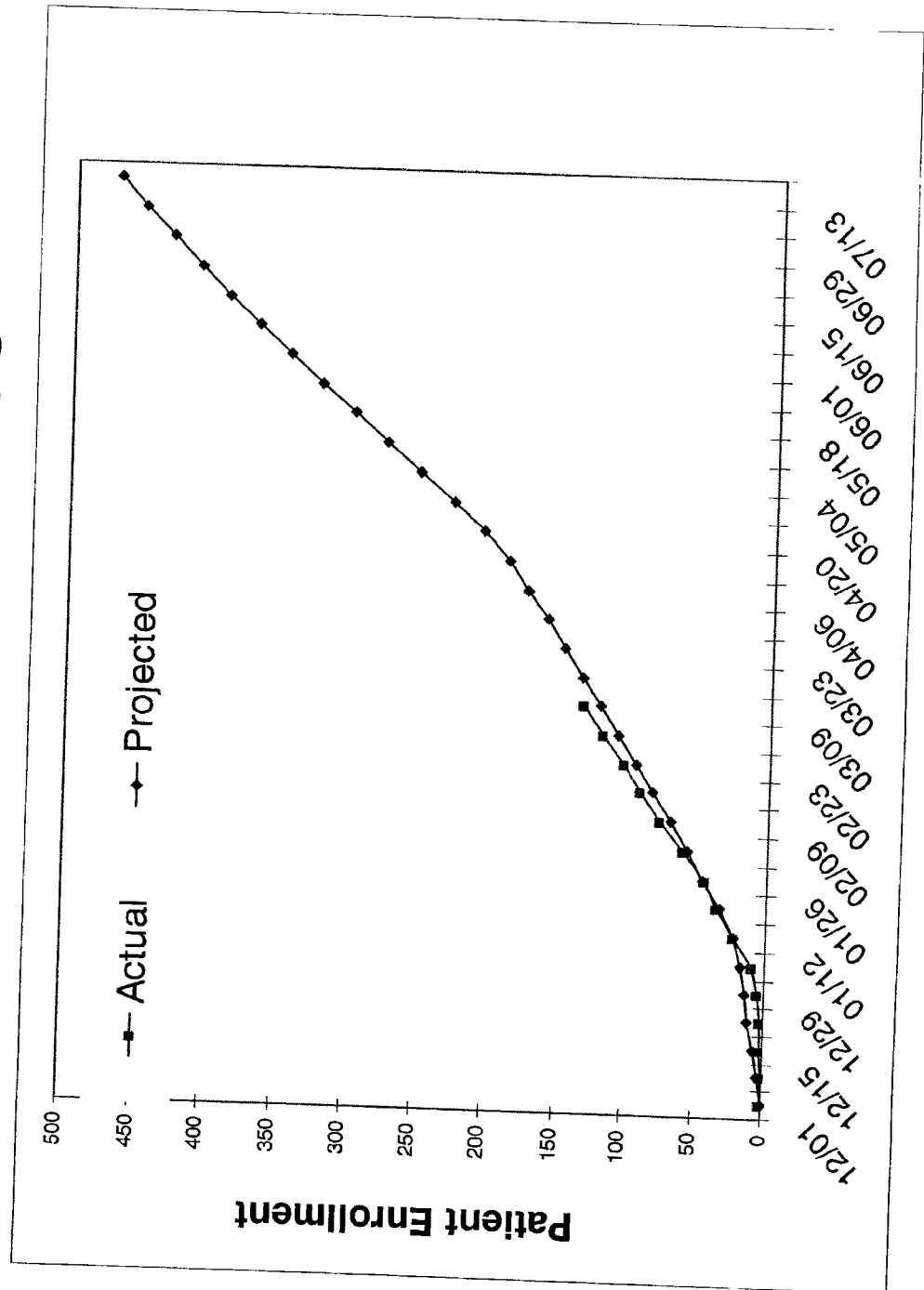
Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-216 ABECB vs Azithromycin	600	Nov. 2000	US	277	110
M00-217 ABECB vs Levofloxacin	500	Jan. 2001	EU	2	100
M00-222 ASP vs Penicillin	520	Jan. 2001	EU	1	45
M00-223 ASP vs Penicillin	520	Nov. 2000	US	337	45

# Phase III: CAP and ABS

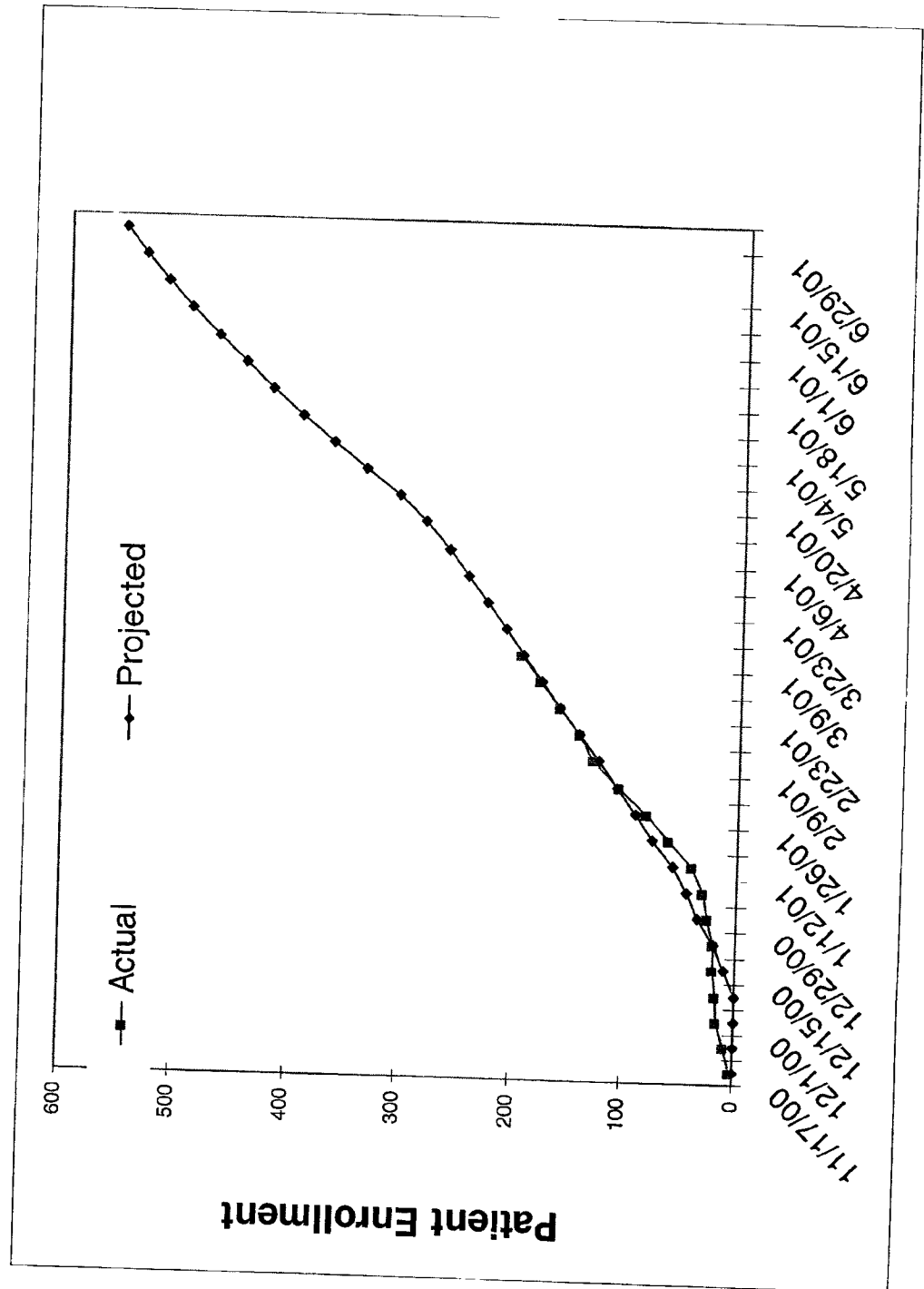
Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-219 CAP 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	143	294
M00-221 CAP vs Levofloxacin	500	Nov. 2001	US		200
M00-220 CAP vs Amoxicillin	500	Nov. 2001	EU		200
M00-225 ABS 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	205	114
M00-218 ABS vs Augmentin	500	Nov. 2001	US		90
M00-226 ABS vs Levofloxacin	500	Nov. 2001	EU		90

# PART 2

# CAP dose-ranging study: enrollment status



# Sinusitis dose-ranging study: enrollment status



# Progress towards resistance claim

Pathogen	M00-216 ABECB	M00-219 CAP	M00-225 ABS
Subjects with Positive culture	266	60	77
<i>S. Pneumoniae</i> isolates	16	16	19
Resistant <i>S.pneumo</i>	7	9	7
<i>Penicillin resist</i>	0	1	1
<i>Macrolide resist</i>	2	0	3
<i>PRSP &amp; MRSP</i>	5	8	3
# of isolates proposed for resistance claim			
PRSP	15	15	15
MRSP	15	15	15

# ABT 773 Contingency Plan

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
- Dose decision delayed to Sept 2001, filing delayed
- Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere

## 2001 Clinical Budget (\$MM)

• 2001 Clinical Program	61.7
• Assumptions to achieve budget	
• Complete 2000/01 Phase III Studies by June 2001 in U.S. and Europe	
• Initiate 2001/02 Phase III Studies by Nov. 2001	
• Conduct start up activities <b>only</b> in Southern Hemisphere, <b>do not</b> initiate enrollment	
• Contingency costs	2.0
• Assumptions	
• Continue European ABECB and ASP studies to Dec 2001	
• Enroll CAP and ABS studies in the Southern Hemisphere through Sept. 2001	
• Partial cost offset due to lower enrollment in U.S. and Europe	



# Other Filing Options

*Other filing options have been evaluated and are less desirable (regulatory, commercial, logistic)*

Option	Indications	Dose	Filing Date US	Filing Date Europe
Option 1 File without CAP indication in the U.S., delay Europe filing	ABECB/ASP/ABS	150mg QD	Aug 2002	June 2003
	CAP	150mg QD or BID	Aug 2003	June 2003
Option 2 Make BID dose decision for CAP and ABS now.	ABECB/ASP	150mg QD	Aug 2002	Aug 2002
	CAP/ABS	150mg BID	Aug 2002	Aug 2002
Option 3 Delay Dose Decision to Phase III	ABECB/ASP/ABS 3 arm CAP Study	150mg QD or BID	Dec 2002	Dec 2002
Option 4 Run separate US and European clinical programs	ABECB/ASP	150mg QD	Dec 2002	Aug 2003
	CAP/ABS	150mg QD US 150mg BID Europe	Dec 2002	Aug 2003

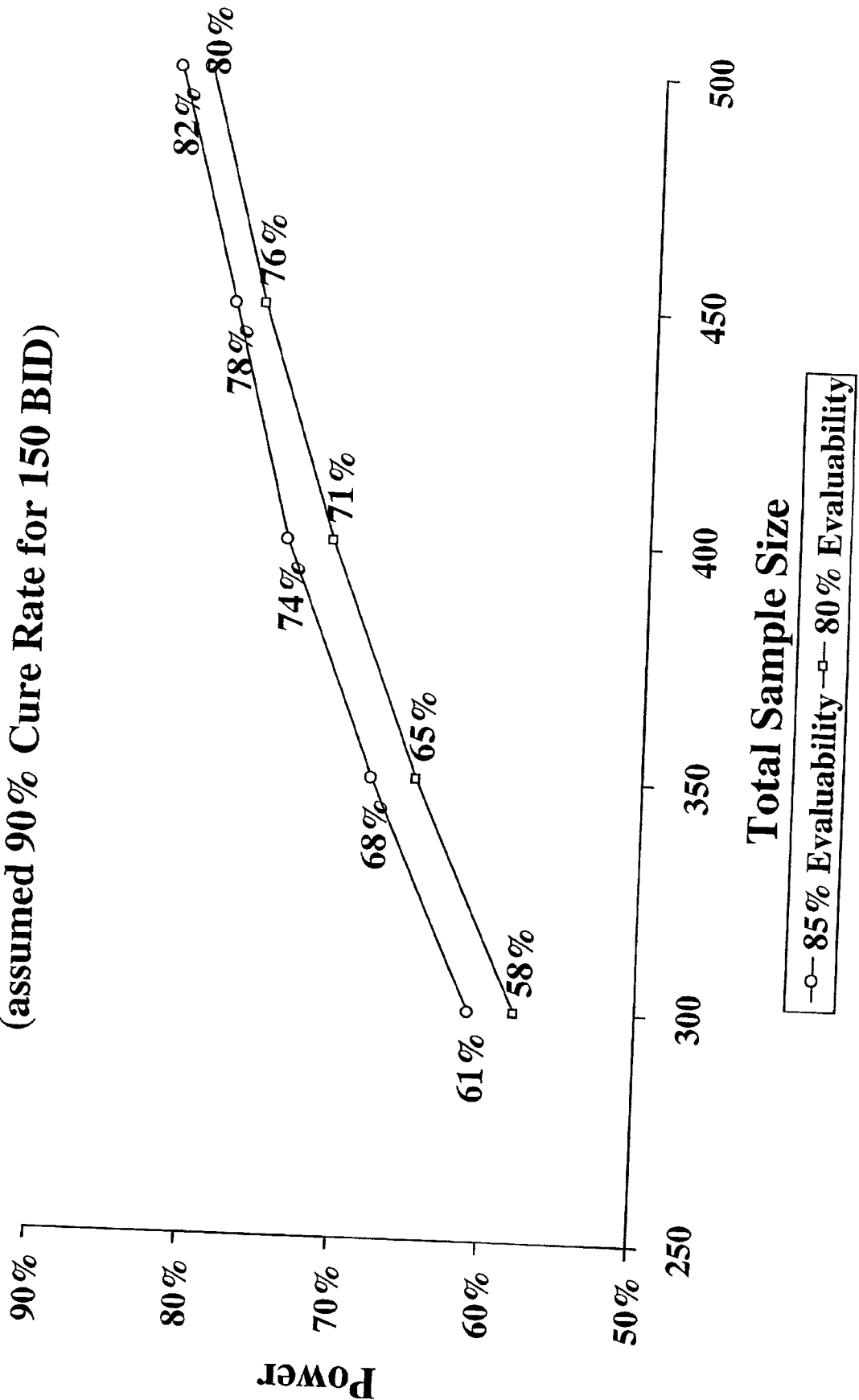
# Possibilities

- Make enrollment targets on time
- A little behind
- Way behind

## Activities-to-date to address CAP enrollment

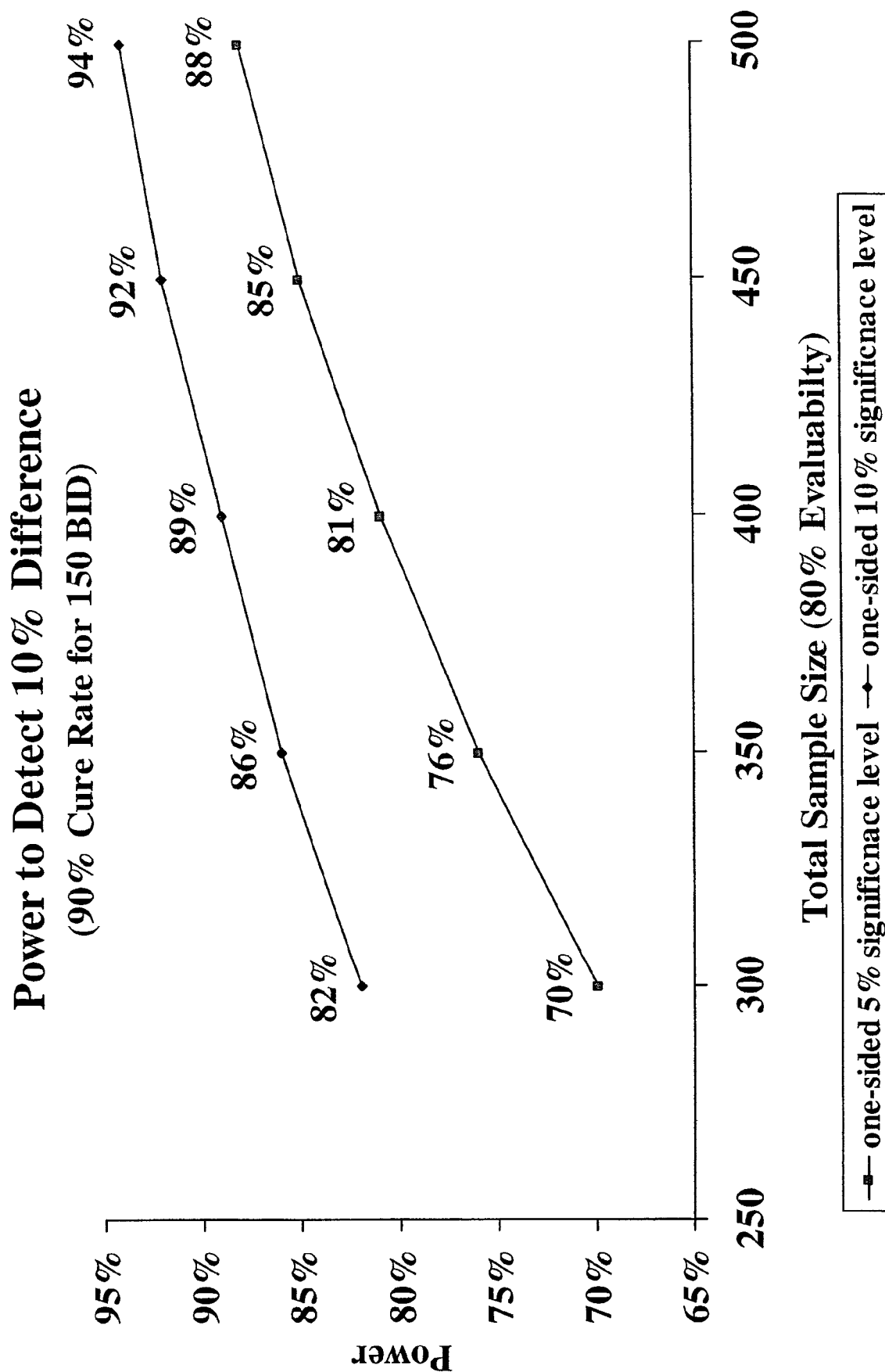
- Increased European sites from 79 to 130 in Nov. 2000
- Site approvals expedited
  - Amendments translated and submitted to Ethics Committees for 350 sites in 1 month
  - CRO actively encouraging investigators to expedite EC approval process as much as possible
- Increased investigator fees
- Increased site follow up/communication
- Diligent CRO management

# Power to Detect 10% Difference (assumed 90% Cure Rate for 150 BID)



# Statistical power is a function of:

- Sample size
- Treatment arm differences
- Level of statistical significance



# Possible outcomes of dose-ranging studies

**QD is:**

CAP	Sinusitis	Decision
Worse	Worse	BID
Same	Worse	BID
Worse	Same	BID or BID/QD
Same	Same	QD

# Agenda

- Market and trends
- Molecule
- Microbiology
- Pharm/tox
  - QT prolongation
  - Hepatotoxicity
- Clinical development
  - Phase I/II summary
  - Dose selection
  - Phase III program
  - Contingency plans
- Timeline and budget
- IV formulation
- Summary of key issues and action plans



## ABT-773 IV Formulation Strategic, Commercial, and Technical Value

- **Strategic Value**
  - IV represents a channel not currently served by Anti-infective Franchise
  - Leverages presence of MCRs and experience with ID community
- **Commercial Value**
  - IV availability improves formulary access to molecule
    - Potential advantage over telithromycin, which will not have an IV
    - Would be competitive with Zithromax, Tequin, Avelox which have IV
  - Positive impact on tablet formulation
    - estimated \$36MM incremental to peak tablet sales due to step-down therapy
    - Enhances overall “potency” image of brand
- **Technical Value**
  - Support for *S. pneumoniae* Resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
  - Provides additional information on QT effects

# ABT-773 IV Planned Clinical Program

- |  |        |
|--|--------|
| • Single Dose-rising Phase I study         | May/01 |
| • Multiple Dose Phase I with selected dose | Aug/01 |
| • File US IND                              | Nov/01 |
| • Initiate Phase III                       | Jan/02 |
| – 2 step-down CAP studies (US/Europe)      |        |
| – 2-3 days dosing                          |        |
| – Two seasons to complete                  |        |
| • Filing                                   | Dec/03 |

- |   |
|---|
| <ul style="list-style-type: none"><li>• IV launch currently lags tablet launch by 1 year</li><li>• further delays will reduce the potential value</li></ul> |
|---|

## IV Development Cost

	Thru 2000	2001	2002	2003 to NDA	Total
Clinical Program	0.2	4.0	6.0	2.5	12.7
Phase I Single Rising Dose		0.5			0.5
Phase I Multiple Dose		0.4			0.4
Phase III 2 step-down CAP Studies (US/Europe)		2.9	6.0	2.5	11.4
CMC	1.0	2.5	1.8	1.3	6.6
Drug Safety/Other	1.0	1.0	1.0	1.0	4.0
Total by Year	2.2	7.5	8.8	4.8	23.3

# Summary: Key Issues

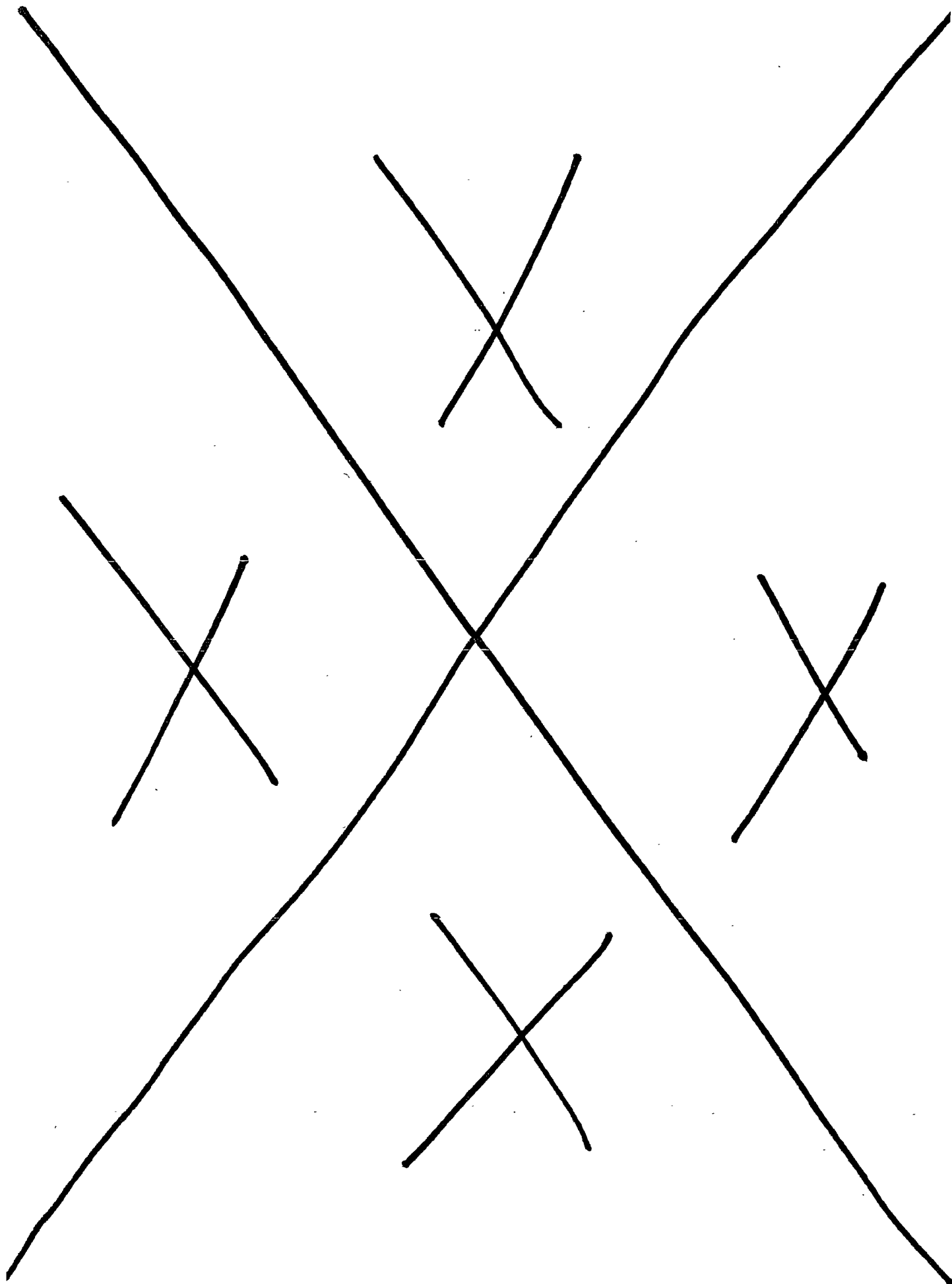
- **QT Prolongation**
  - Possible class labeling, with resulting safety perception
- **Resistance claim**
  - Key differentiating feature
  - Bacteremic isolates requested by FDA requires IV
- **IV Formulation**
  - Strengthens strategic, commercial, and technical value of product
- **QD vs BID dosing**
  - Divergence regulatory and commercial considerations in US vs Europe
- **Delayed Phase III program**
  - Delayed dose selection decision beyond July/Aug 2001 could delay filing

# ABT-773 Action Plans

Key Issue	Action Plans
<b>QT Prolongation</b>	<ul style="list-style-type: none"> <li>▪ Conduct EKG monitoring in Phase III to gather additional data on QT prolongation</li> <li>▪ Anticipate and fulfill regulatory expectations for animal and human data</li> </ul>
<b>Resistance claim</b>	<ul style="list-style-type: none"> <li>▪ Accrue sufficient patients to obtain necessary organisms</li> <li>▪ IV formulation would access bacteremic patients</li> </ul>
<b>IV Formulation</b>	<ul style="list-style-type: none"> <li>▪ Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding</li> </ul>

# ABT-773 Action Plans

Key Issue	Action Plans
<b>QD vs BID dosing</b>	<ul style="list-style-type: none"> <li>▪ Select dose based on outcome of current QD vs BID trials</li> <li>▪ Minimize regulatory risk</li> <li>▪ Optimize global commercial opportunity</li> </ul>
<b>Delayed Phase III program</b>	<ul style="list-style-type: none"> <li>▪ CAP Study sites increased in the US and Europe from 209 to 300 sites</li> <li>▪ Southern hemisphere contingency</li> <li>▪ Re-evaluate other contingency plans</li> </ul>







# **Project Review**

## **ABT-089 and ABT-594**

### **February 2, 2001**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002314**

# Project Review

- ABT-089

REDACTED

- ABT-594

- Overview, upcoming milestone: June 2001
- Follow-on strategy

HIGHLY  
CONFIDENTIAL

ABBT 0002315

# **Neuronal Nicotinic Receptor (NNR) Program**

- Scientific leadership position for Abbott
- An emerging diversity of receptors
- Multiple potential therapeutic targets

**ABT-089**

**REDACTED**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002317**

**ABT-089**

**REDACTED**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002318**

# ABT-594

## *Overview*

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

# ABT-594

*Therapeutic Utility*

Neuropathic Pain

Chronic Pain

Cancer Pain

Diabetic  
Neuropathy

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ABBT 0002320

REDACTED

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ABBT 0002321



**REDACTED**

REDACTED

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ABBT 0002323

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**ABBT 0002367**

REDACTED

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ABBT 0002358

# **ABT-594 Project Review February 2, 2001**

## **Introduction**

**Chris Silber**

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**ABBT 0002359**

# ABT-594 Project Review

## *Agenda*

- |                           |                  |
|---------------------------|------------------|
| • Introduction            | Chris Silber     |
| • Pharmacological Profile | Jim Sullivan     |
| • Clinical Overview       | Bruce McCarthy   |
| • Commercial Assessment   | Andrea Landsberg |
| • Go/No Go Process        | Bruce McCarthy   |
| • Follow-On Strategy      | Mike Meyer       |

# ABT-594

## *Overview*

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM



## Pain Prevalence

- 22% primary care patients worldwide have persistent pain
- Neuropathic pain
  - 20% of diabetics
  - 40% of HIV infected
  - 36% of cancer patients

# Pain Therapeutics Market

- \$12 billion in sales of key classes (NSAIDs, COX-2s, opioids, non-opioids)
- \$700 million in sales of key neuropathic pain compounds
  - use largely off-label
  - low cost generics

# Neuropathic Pain

## *Treatment*

### Some efficacy

(at best 40% vs. 20% placebo)

- Tricyclic antidepressants
  - Amitriptyline, desipramine, etc.
- Anti-epileptic drugs
  - Carbamazepine
  - Gabapentin (Pregabalin)
  - Topiramate, others
- Sodium channel blockers
  - Lidocaine
- Opioids
  - Tramadol

### No efficacy

- SSRIs
- NSAIDs/COX-2

# **Broad-Spectrum, Non-Opioid Analgesic Activity by Selective Modulation of Neuronal Nicotinic Acetylcholine Receptors**

A.W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon,  
D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz,  
A. H. Dickenson, R. D. Porsolt, M. Williams, S. P. Arneric

SCIENCE • VOL. 279 • 2 JANUARY 1998

# Development Strategy

## Acute

Post-dental surgery  
Sprains and strains  
Acute back pain  
Trauma  
Post-general surgery  
Post-orthopedic surgery  
Dysmennorrhea  
Renal colic  
Biliary colic  
Pancreatitis  
Infections

## Neuropathic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug-induced polyneuropathy  
HIV predominantly sensory neuropathy  
Back pain  
Cancer pain  
Trigeminal neuralgia  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
Complex regional pain syndromes (I, II)  
Atypical facial pain  
Phantom limb pain

## Chronic Nociceptive

Osteoarthritis  
Chronic back pain  
Rheumatoid arthritis  
Cancer pain  
Fibromyalgia  
Sickle cell disease  
TMJ disorder  
Bursitis  
Tendinitis  
Chronic visceral pain

# Development Strategy

*Choose Portals of Entry*

**Molar Extraction** → **Acute Pain**

**Peripheral Neuropathy** → **Neuropathic Pain**

**Osteoarthritis** → **Chronic Nociceptive Pain**

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# ABT-594

## *Current Label Target*

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

### Upside Claim

- Neuropathic Pain
- Post herpetic neuralgia
- OA Pain
- Chronic Pain
- Cancer Pain

### General Pain Claim

- Not viable due to 1.5 hour onset

# ABT-594

## *Go/No Go Process*

- Decision analysis (DSG) will be used as a tool to determine milestone criteria
  - Efficacy and safety
  - Titration effects
  - Dose selection
  - Indications
  - Market research



# ABT-594

## *Phase III Clinical Plan*

	U.S.	Europe	Japan
Diabetic neuropathy	2 (n=1200)	2 (n=1200)	1 (n=300)
Long-term safety	1 (n=500)	1 (n=500)	-
Gabapentin comparator	-	1 (n=320)	-
Other neuropathic pain (Phase 3B) post herpetic neuralgia, sciatica	2 (n=600)	-	-

	<u>01</u>	<u>02</u>	<u>03</u>	<u>Total</u>
Cost (\$ million)	6.1	59.6	55.7	121.4

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# ABT-594

## *Phase 2 to 3 Transition*

Milestone review	6/01
End of Phase 2 package/request	9/01
Start manufacture Phase 3 supplies	9/01
Ship first Phase 3 supplies	2/02
Initiate Phase 3	3/02
Regulatory filings	9/03

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# ABT-594

## *Overview*

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- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

**ABT-594 Project Review  
February 2, 2001  
Pharmacological Profile**

**Jim Sullivan**

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**ABBT 0002373**

# ABT-594: Preclinical Pharmacology

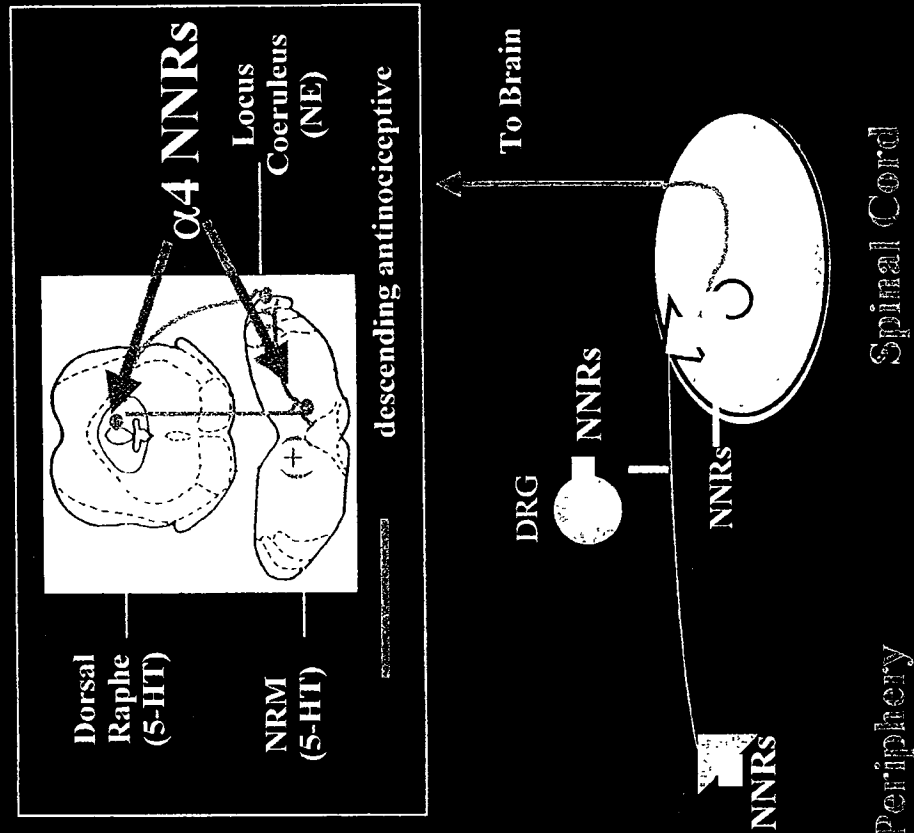
- Rationale for NNRs and pain
  - Knockout, antisense and pharmacological validation
- *in vitro* and *in vivo* profile of ABT-594
  - Efficacy
  - Safety

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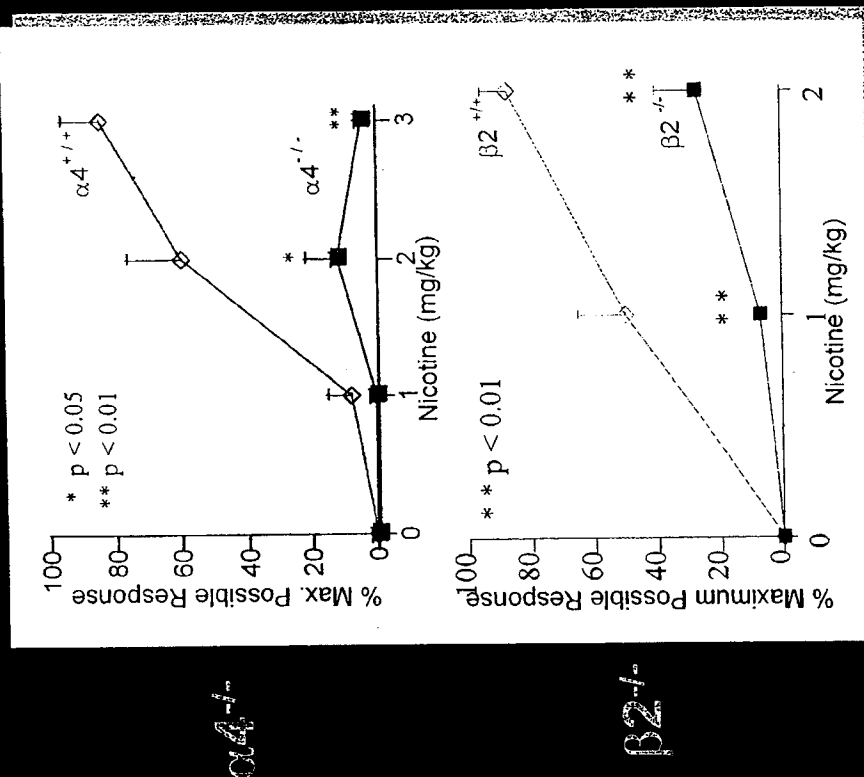
# NNRs and Pain: NNRs are Expressed in Pain Pathways

- CNS
  - $\alpha 4$  NNRs are localized in NRM and dorsal raphe (Key CNS pain center)
- Spinal Cord
  - NNRs are expressed in dorsal horn neurons (key spinal cord pain processing center)
- Sensory Neurons
  - $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 7$  NNRs are expressed in DRG and on central and peripheral C-fiber nociceptors



# NNRs for Pain: Role of $\alpha 4$ and $\beta 2$ NNRs Established Using Knockout Mice

- In either  $\alpha 4^{-/-}$  or  $\beta 2^{-/-}$  mice, neither nicotine nor epibatidine was active in the hot plate assay (supraspinal mechanism)



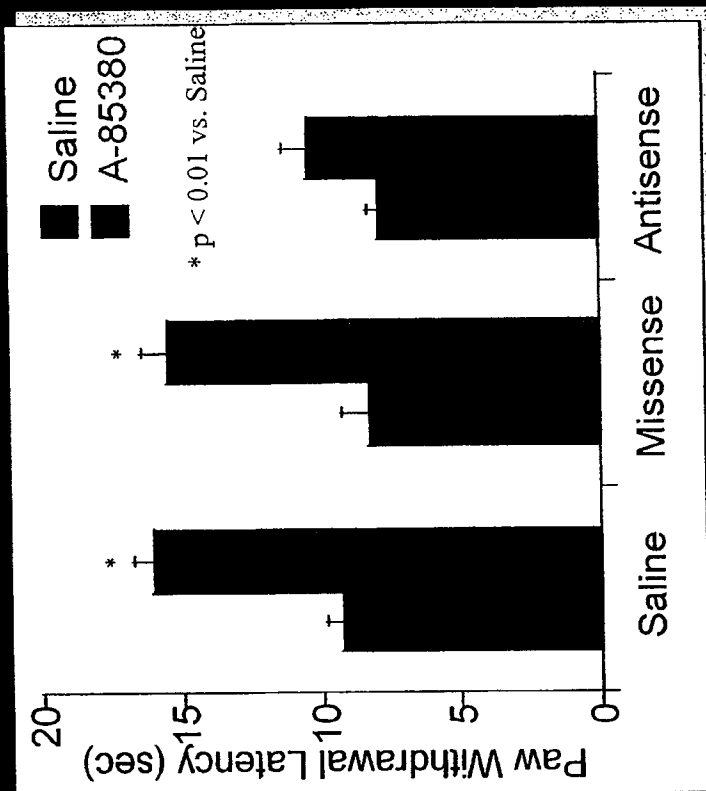
Marubio, et al. *Nature* 1999 398, 805-810.

# NNRs for Pain: Target Validation Using $\alpha 4$ Antisense

## *$\alpha 4$ Antisense Treatment Attenuates Antinociception in the Hot Box Model of Acute Thermal Pain*

• Rats received either a saline, missense, or antisense continuous i.c.v. infusion (0.75 nmol/hr) for 7 days

• Rats were evaluated in a crossover design in the hot box model of acute thermal pain



Bitner, et. al, Brain Res. 871: 66, 2000

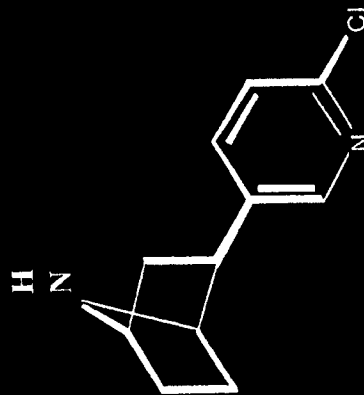


# Target Validation: NNR Agonists Are Analgesic

- NNR agonists are -
  - Antinociceptive (capable of raising nociceptive thresholds in naïve animals)
  - Antihyperalgesic (capable of reversing the reduction in nociceptive thresholds following injury)

- Epibatidine (key discovery)

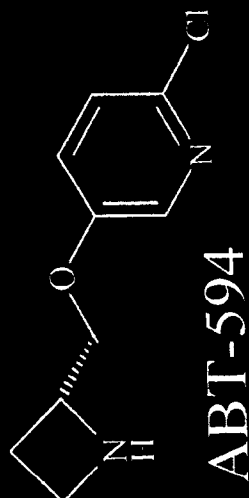
- 200x more potent than morphine
- Non-opioid
- Potent NNR agonist
- BUT highly toxic



Radio and Daly, *Mol. Pharmacol.*  
45: 563, 1994.

# NNRs and Pain: ABT-594

*Goal*



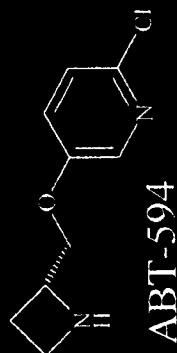
- Maintain broad spectrum analgesic efficacy of epibatidine
  - Maintain potency at  $\alpha 4$  containing NNRs
- Decrease side-effect liabilities by decreasing activity at
  - Neuromuscular junction nicotinic receptors ( $\alpha 1 \beta \delta \gamma$ )
  - Ganglionic NNR subtypes ( $\alpha 3 \beta 4$ ,  $\alpha 5 \beta 2 \beta 4$ )

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# ABT-594 is a More Selective NNR than Epibatidine in Radioligand Binding Studies

Binding Site (K <sub>i</sub> ; nM)	Epibatidine	ABT-594
Cytisine Binding Site ( $\alpha 4\beta 2$ )	0.042	0.037
BTX Binding Site (Peripheral) ( $\alpha 1$ )	2.4	16,600

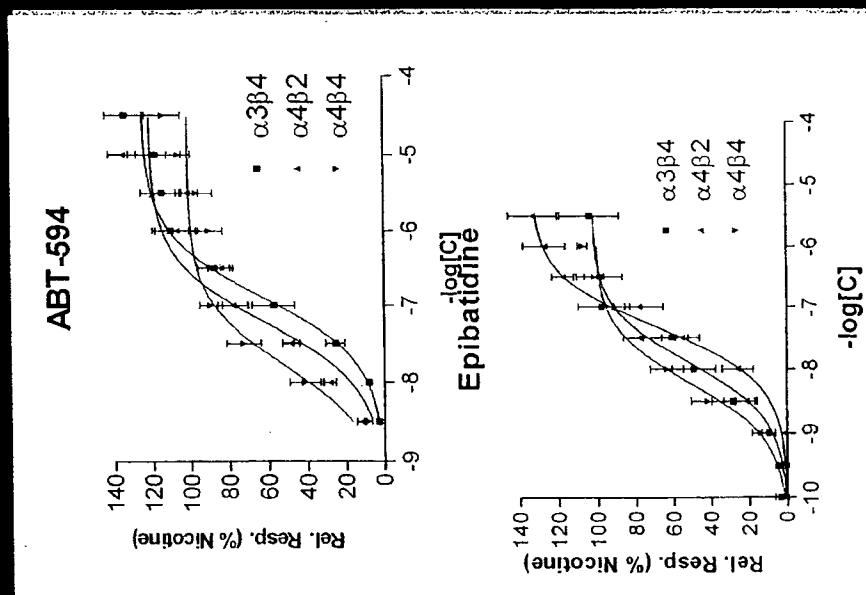


- ABT-594 retains potency of epibatidine at the  $\alpha 4\beta 2$  binding site
- ABT-594 is > 5000-fold less potent than epibatidine at the peripheral neuromuscular junction nicotinic receptor

# In Vitro Functional Profiles of ABT-594 and Epibatidine

## Functional Activity

- Rank order of potency
  - ABT-594:  $\alpha 4\beta 4 \sim \alpha 4\beta 2 > \alpha 3\beta 4$
  - Epibatidine:  $\alpha 4\beta 4 \sim \alpha 3\beta 4 \sim \alpha 4\beta 2$
- ABT-594 displays modest  $\alpha 4$  vs  $\alpha 3\beta 4$  selectivity
  - Compounds with greatly improved selectivity have been identified

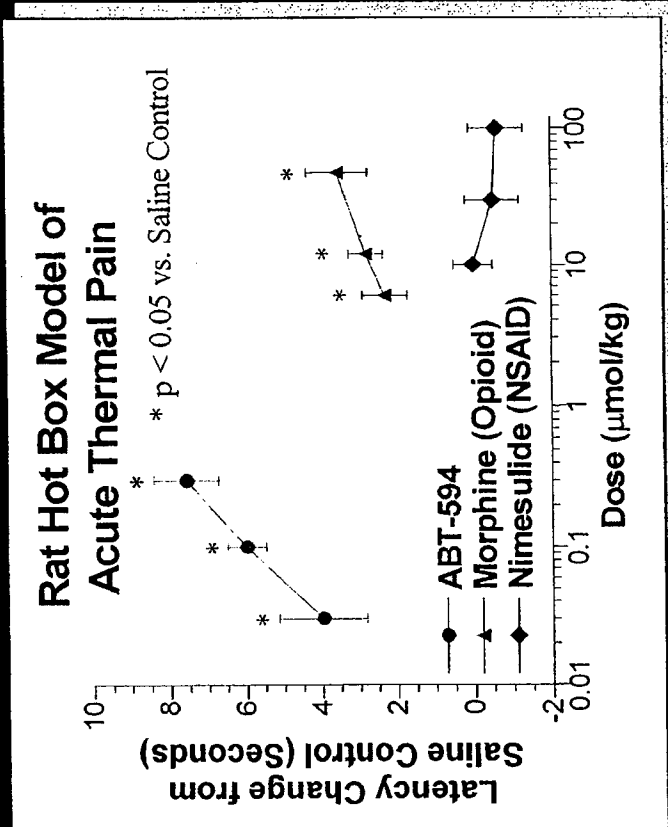


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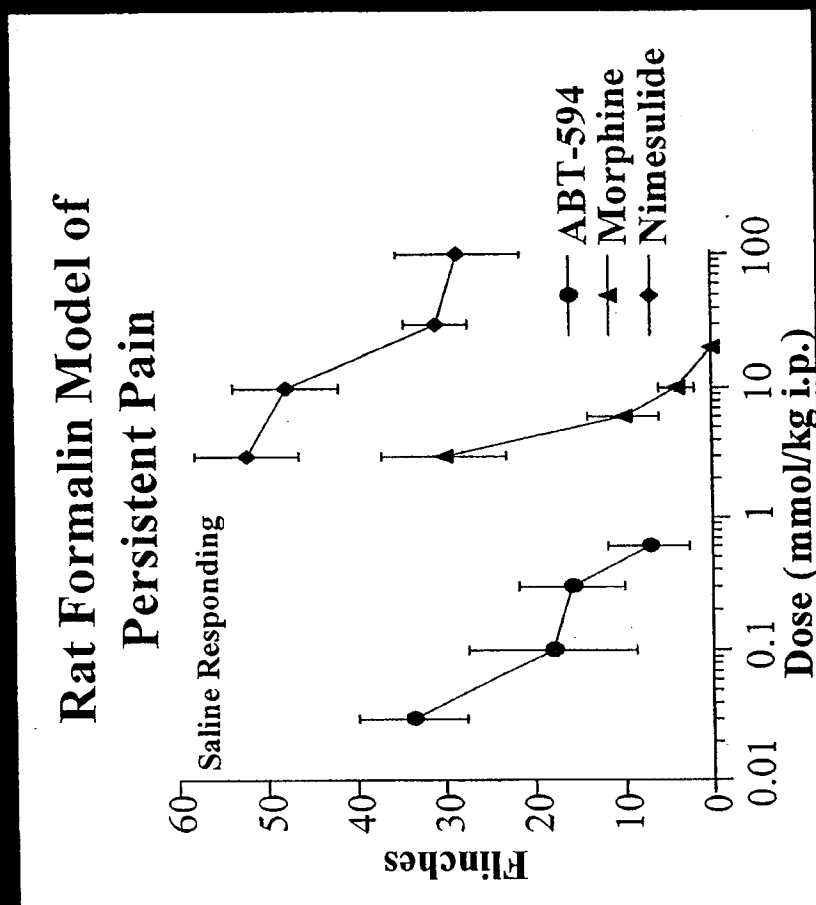
# ABT-594: In Vivo Efficacy in Models of Acute Thermal Pain

- ABT-594 is potent and efficacious in the Hargreaves Hot Box model of thermal nociception
- Onset of Efficacy = < 30 min
- Duration of efficacy ~ 2 hrs
- The effects of ABT-594 are blocked by the nicotinic antagonist mecamylamine, but not by the opioid antagonist naloxone



# ABT-594: In Vivo Efficacy in Models of Persistent Pain

- ABT-594 exhibits comparable efficacy and 50-fold greater potency than morphine in Phase II of the formalin model of persistent chemical pain
- ABT-594 is active upon both i.p. and oral administration

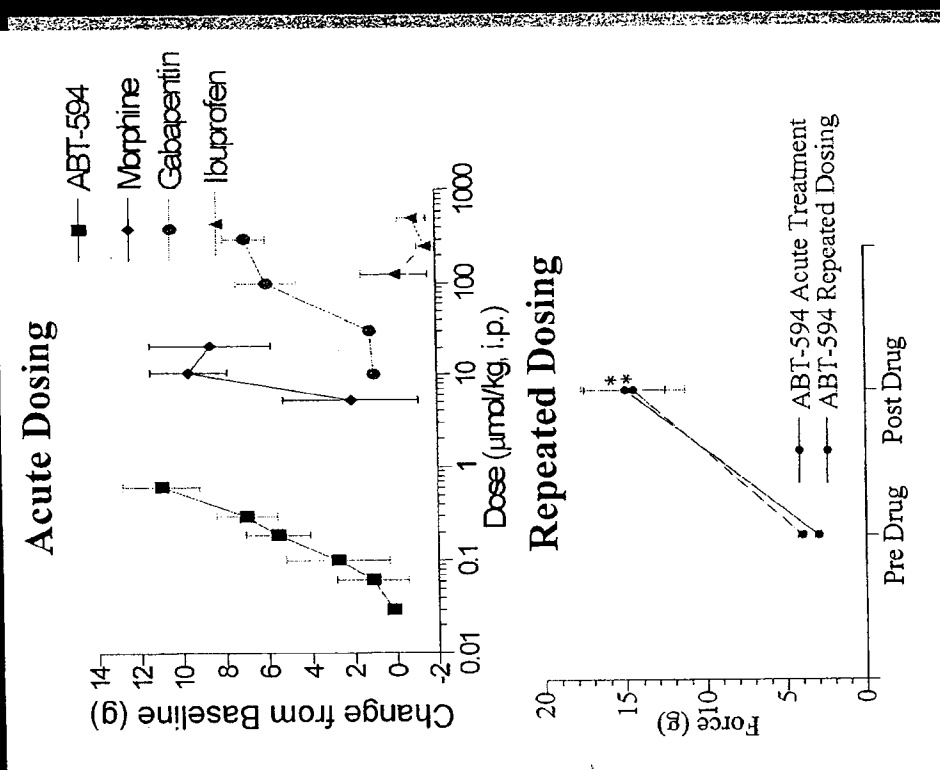


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# ABT-594: In Vivo Efficacy in Models of Neuropathic Pain

- ABT-594 exhibits comparable efficacy and enhanced potency vs. known efficacious agents in models of neuropathic pain
- Efficacy observed at ~ 3 ng/ml
- ABT-594 retains efficacy following repeated administration
- Efficacy observed in rodent model of diabetic polyneuropathy



# ABT-594: Efficacy vs. Other Analgesics

	Inflammatory Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 $\mu$ mol/kg)	+++ (0.1 $\mu$ mol/kg)	+++ (0.03 $\mu$ mol/kg)
Celecoxib	++ (30 $\mu$ mol/kg)	+ (30 $\mu$ mol/kg)	0
Morphine	+++ (3 $\mu$ mol/kg)	+++ (10 $\mu$ mol/kg)	++ (3 $\mu$ mol/kg)

+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.



## How do NNR Agonists Produce Analgesia?

- Mouse knockouts support role of  $\alpha 4$  and  $\beta 2$ 
  - Key differences between pain type
- Role for  $\alpha 4$  subtype in acute thermal pain (activation of descending inhibitory pathways)
  - Antisense studies
  - Site injection studies
  - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

## ABT-594: Preclinical Assessment of Side Effect Liabilities

- Emesis
  - Emesis observed in monkey at 9x efficacious plasma levels
  - Emesis observed in dogs at efficacious plasma levels
  - Ferret model developed in response to early clinical data
    - Correlation established between activity at  $\alpha 3\beta 4$  NNRs and emesis
- CV
  - No effects on hemodynamics at 30X efficacious plasma levels
- Dizziness: no validated preclinical models exist
  - Effects on balance, coordination and muscle strength (Edge Test) observed following acute but not repeated dosing
- ABT-594 displays a reduced propensity for morphine-like side effects of:
  - Constipation
  - Respiratory Depression
  - Sedation

## **ABT-594: Summary of Preclinical Findings**

- ABT-594 is effective across a broad range of preclinical models of acute, persistent and neuropathic pain
- ABT-594 retains efficacy upon repeated dosing
- The antinociceptive properties of ABT-594 are modulated via activation of NNRs and not via opioid receptors
- Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
  - Constipation
  - Respiratory depression
  - Sedation
- Preclinical studies suggest that ABT-594 will have an improved side-effect profile relative to nicotine

# **ABT-594 Project Review February 2, 2001**

## **Clinical Overview**

**Bruce McCarthy**

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**ABBT 0002389**

# ABT-594

## *Take Home Messages*

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
  - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

**ABT-594**

**Definitely NOT a take home  
message for today:**

*ABT-594 will satisfy the unmet medical need  
in pain management*

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# ABT-594

## Clinical development

### ❖ Current pain management

- Development strategy: bench to bedside
- Clinical trial results

# Classification of Pain

## Pain Categories

### Noiceptive

#### Acute

Post-dental & post-surgical Pain  
Trauma  
Pancreatitis  
Infections

#### Chronic

Osteoarthritis  
Rheumatoid arthritis  
Fibromyalgia  
Chronic viscearal pain

### Neuropathic

#### Acute

Compression neuropathy

#### Chronic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug induced polyneuropathy  
HIV predominantly sensory neuropathy  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
CRPS type I and II  
Atypical facial pain  
Phantom limb pain

Cancer pain  
Back pain



# Classification of Pain

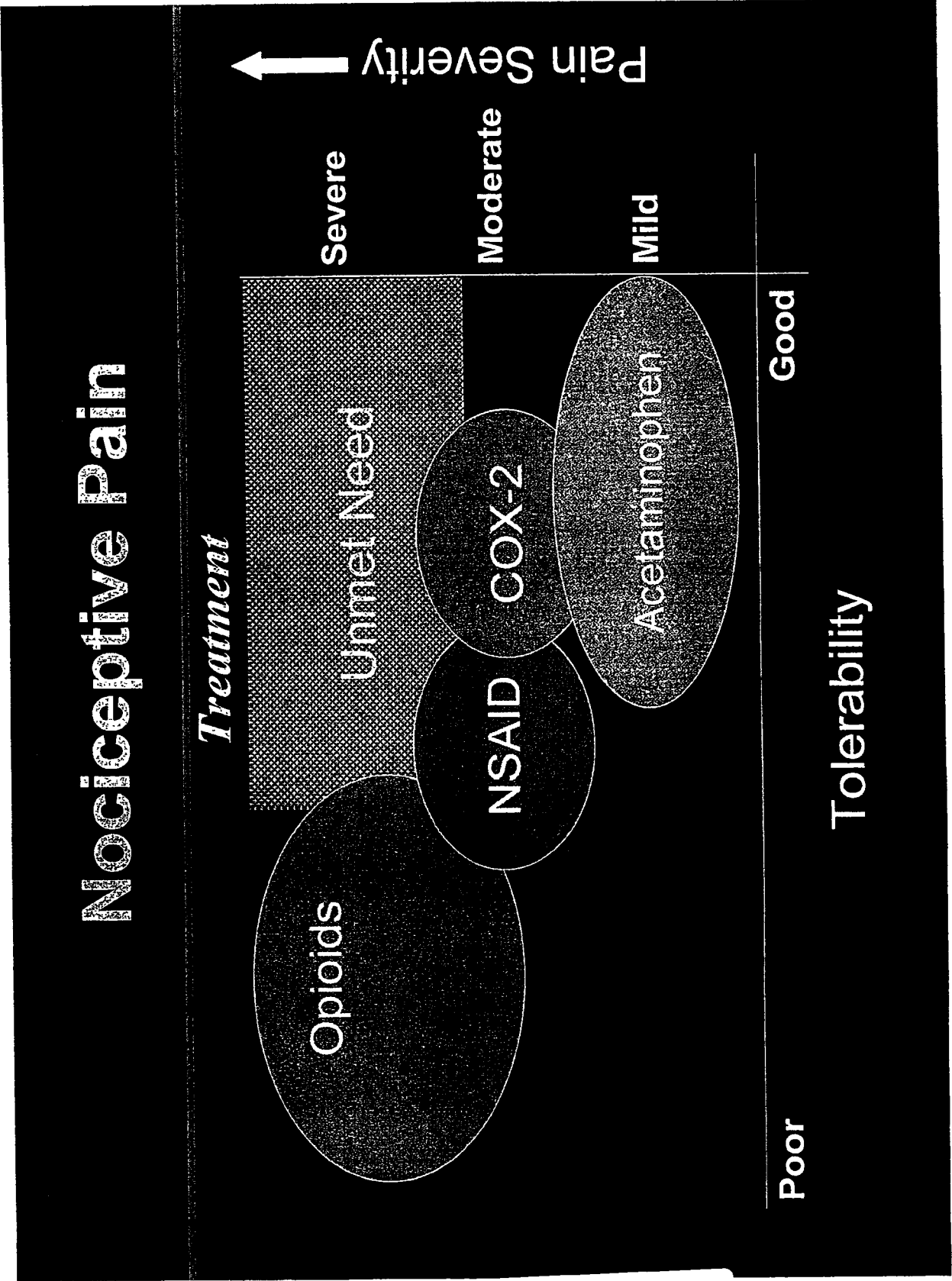
## *Pain Epidemiology*

- **Chronic pain**

- 20% U.S. population: any chronic
- 22% worldwide: persistent pain

- **Neuropathic pain**

- 20% of diabetics
- 40% of HIV infected
- 36% of cancer



# Nociceptive Pain

## Treatment Adverse Events

OxyContin  
Osteoarthritis  
20 mg q12

OxyContin<sup>2</sup>

Ultram<sup>1</sup>  
50-100 mg

Event

Somnolence

N/A

23 %

27 %

Dizziness

31 %

13 %

20 %

Nausea

34 %

23 %

41 %

Vomiting

13 %

12 %

23 %

Constipation

38 %

23 %

32 %

Pruritis

N/A

N/A

16 %

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

N/A - Not Available

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# Neuropathic Pain

## *Overview*

- **Characteristic symptoms**

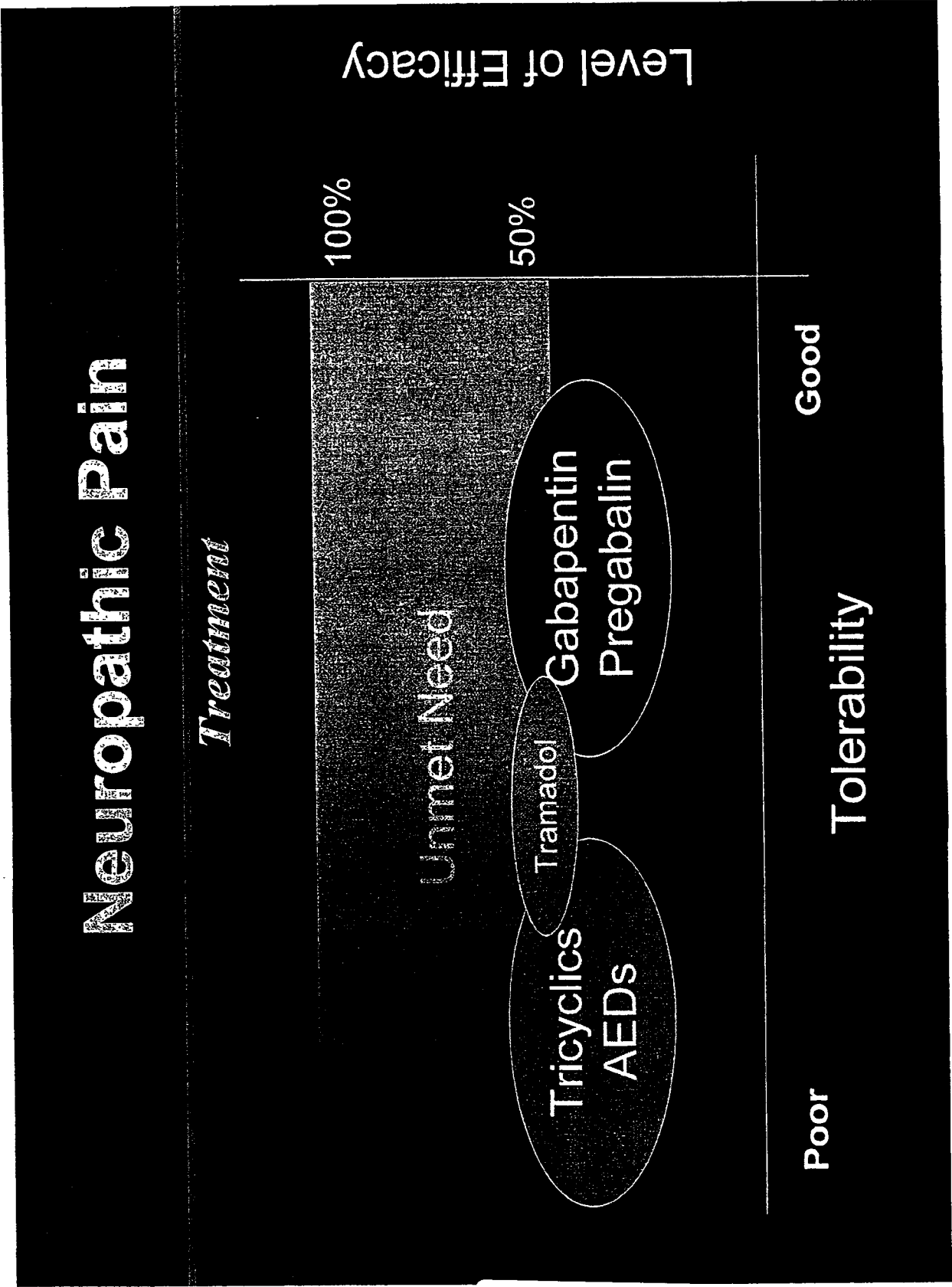
- Spontaneous: dysesthesia, shooting pains
- Evolved: allodynia, hyperpathia

- **Pathophysiology**

- Associated with peripheral nerve injury
- Abnormalities develop over time in the PNS and CNS

- **Treatment**

- Tricyclic and other “antidepressants”
- Antiepileptic drugs
- Sodium channel blockers (lidocaine)
- Opioids
- All minimally effective



# Neuropathic Pain

## Treatment Adverse Events Rates

Event      Amitriptyline  
150 mg/d<sup>1</sup>      Carbamazepine  
600 mg/d      Gabapentin  
3600 mg/d      Pregabalin  
300 mg/d

Confusion	N/A	N/A	8%	5%
Somnolence	66%	53%	23%	24%
Dizziness	28%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

<sup>1</sup> Max, 1987 (n=29)  
N/A - Not Available

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# ABT-594

## Clinical development

- Current pain management

## Development strategy: bench to bedside

- Clinical trial results

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ABBT 0002400

# ABT-594

## *Proof of Principle*

**What characterizes an innovative analgesic?**

Spectrum of activity

Time of onset/duration

Level of efficacy

Safety/efficacy ratio



# PART 2

# ABT-594

## *Spectrum of Activity: Where to Start?*

### Acute

Post-dental surgery  
Sprains and strains  
Acute back pain  
Trauma  
Post-general surgery  
Post-orthopedic surgery  
Dysmennorrhea  
Renal colic  
Biliary colic  
Pancreatitis  
Infections

### Neuropathic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug-induced polyneuropathy  
HIV predominantly sensory neuropathy  
Back pain  
Cancer pain  
Trigeminal neuralgia  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
Complex regional pain syndromes (I, II)  
Atypical facial pain  
Phantom limb pain

### Chronic Nociceptive

Osteoarthritis  
Chronic back pain  
Rheumatoid arthritis  
Cancer pain  
Fibromyalgia  
Sickle cell disease  
TMJ disorder  
Bursitis  
Teninitis  
Chronic visceral pain

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ABBT 0002402

# ABT-594

## *Choose Portals of Entry*

Molar

Extraction

Acute Pain



Peripheral

Neuropathy

Neuropathic Pain



Osteoarthritis

Chronic Nociceptive  
Pain



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ABBT 0002403

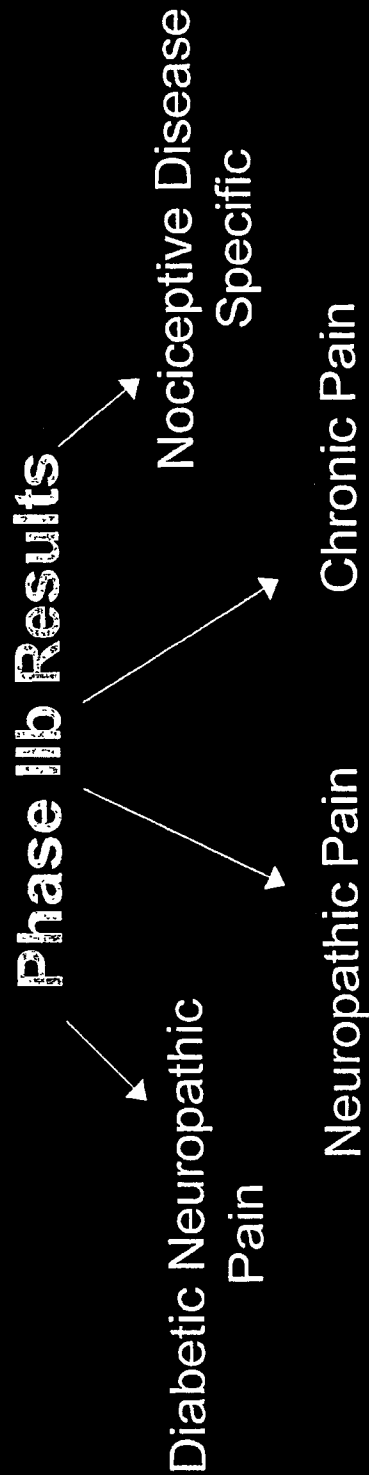
# ABT-594

## *Initial Profile*

- **Preclinical promise**
  - Efficacy for all types of pain
  - Challenges
- **Current characteristics**
  - Analgesic potential demonstrated in molar extraction, neuropathic pain and osteoarthritis
  - Onset ( $T_{\max}$ , tolerability) appears to exclude rapid relief of pain (“acute pain”)

# ABT-594

## *Future Regulatory Strategy*



### +/- Publication Strategy/Phase IV (e.g.)

- Post-herpetic neuralgia
- Nociceptive pain
  - Osteoarthritis
  - Low back pain

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ABBT 0002406

# ABT-594

## Clinical development

- Current pain management
- Development strategy: bench to bedside

## ❖ Clinical trial results

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ABBT 0002406

# ABT-594

## *Pharmacokinetics and Metabolism*

- Half-life ( $t_{1/2}$ ): about 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{\max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{\max}$  similar with/without food
- $T_{\max}$  varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

# **ABT-594**

**ABT-594's analgesic potential demonstrated in:**

**Molar Extraction**

**Neuropathic Pain**

**Osteoarthritis**

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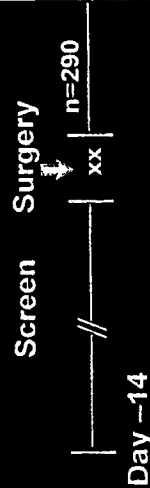
**ABBT 0002408**



# Molar Extraction Study

## Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo
Single dose	

- Third molar extraction

- Outcome measures:


Pain relief (PR)

Categorical scale:

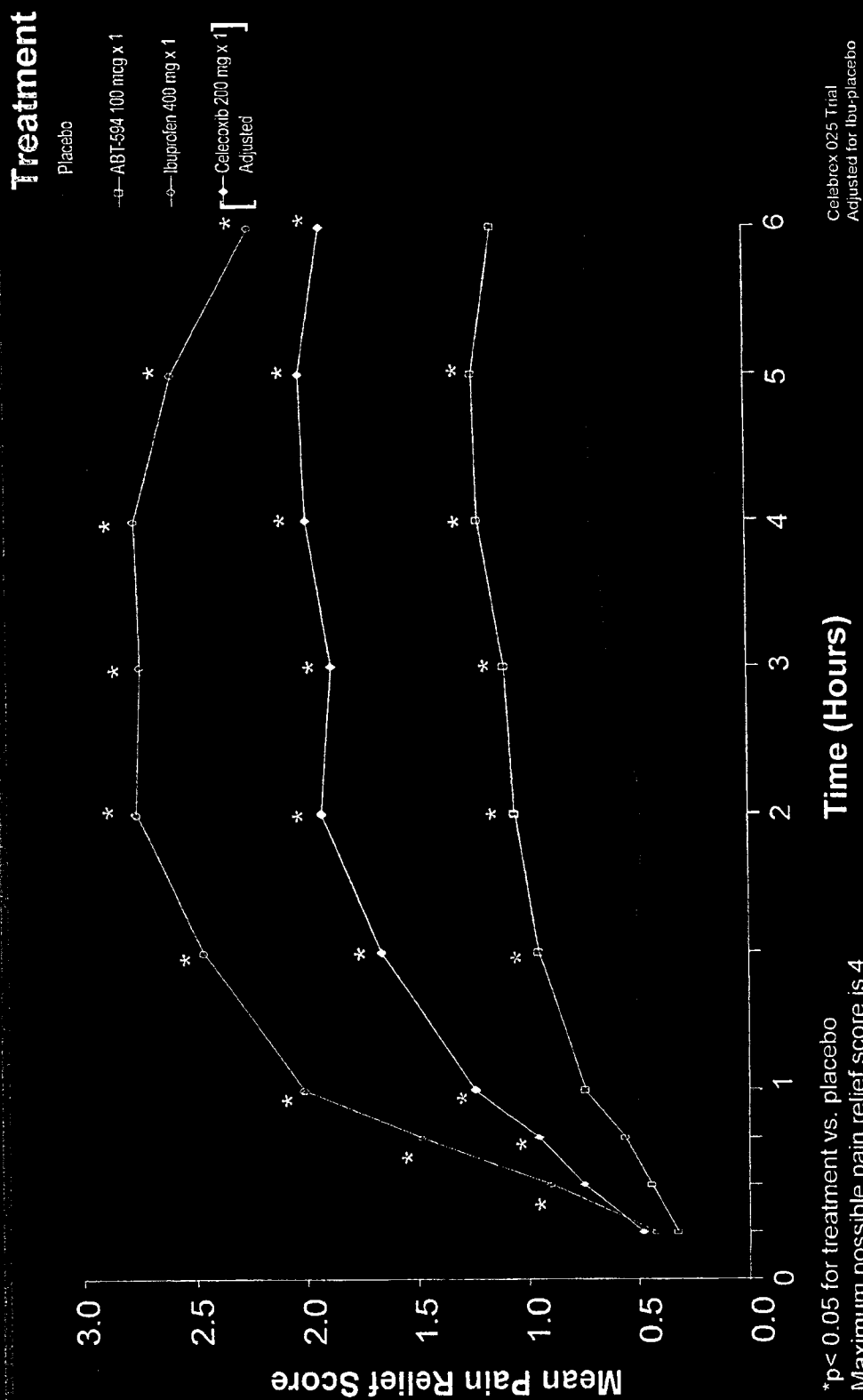
- |  |      |          |      |       |          |
|--|------|----------|------|-------|----------|
|  | 0    | 1        | 2    | 3     | 4        |
|  | none | a little | some | a lot | complete |
- Power: 70% to detect an effect similar to acetaminophen plus codeine
  - Solution

# Molar Extraction Study

## Outcome Measures

- **Pain Relief (PR)**
  - Categorical scale: 0 none 1 a little 2 some 3 a lot 4 complete
- **Total Pain Associated Relief (TOTPAR)**
  - Area under the curve for PR (0-6 hours)
- **Pain Intensity (PI)**
  - Categorical scale: 0 none 1 mild 2 moderate 3 severe
  - Visual Analog Scale
 
- **Stop Watch Model**
  - Time to "perceptible" and "meaningful" relief
- **Time To Rescue Medication**
- **Patient Global**
  - Rate medication: 1 poor 2 fair 3 good 4 excellent

# ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



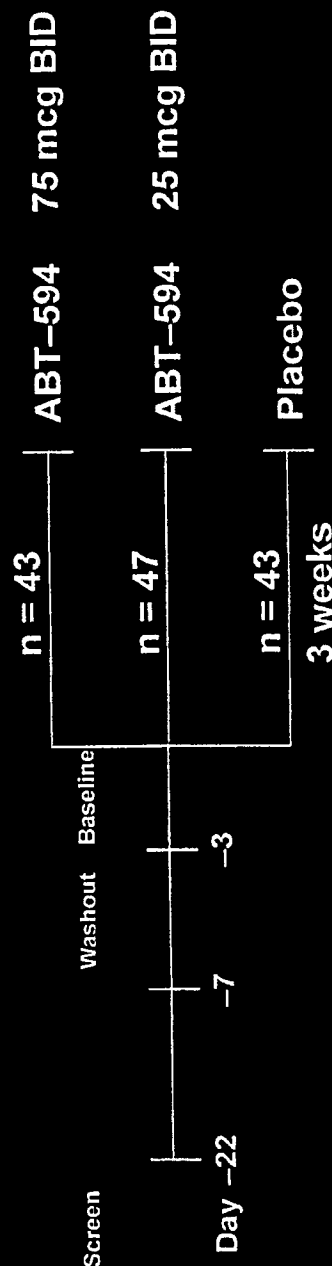
HIGHLY  
CONFIDENTIAL

ABBT 0002411

# Neuropathic Pain Pilot

## *Design*

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
  - 52% idiopathic
  - 46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

HIGHLY  
CONFIDENTIAL

ABBT 0002412

# Neuropathic Pain Pilot

## Outcome Measures

### • Pain Intensity (PI)

- Categorical Scale:
- |      |      |          |        |
|------|------|----------|--------|
| 0    | 1    | 2        | 3      |
| none | mild | moderate | severe |
- 
- Visual Analog Scale: (0-100 mm)
- |         |                |
|---------|----------------|
|         |                |
| no pain | worst possible |

### • Neuropathic Pain Scale (NPS)

- 10 items (e.g., sharp, hot, intense), for total 0-100 points
- Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

The most sharp sensation imaginable ("like a knife")

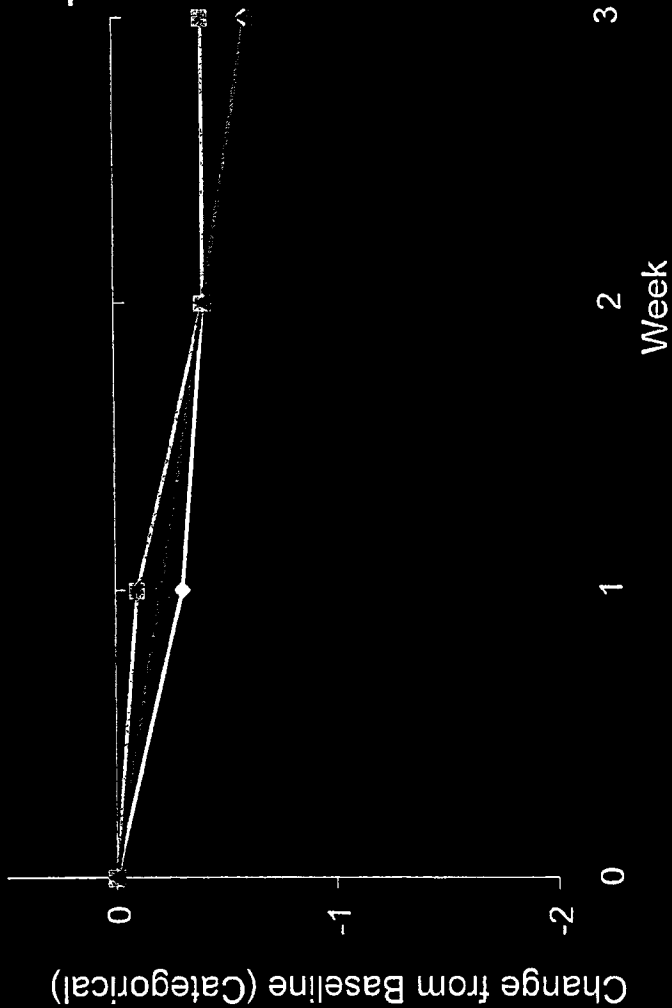
not sharp	1	2	3	4	5	6	7	8	9	10
-----------	---	---	---	---	---	---	---	---	---	----

### • Patient Global (PG)

- Rate Medication:
- |      |      |      |           |
|------|------|------|-----------|
| 1    | 2    | 3    | 4         |
| poor | fair | good | excellent |

# ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared to Placebo in Neuropathic Pain

Treatment	Change: Baseline to Final
Placebo	↓ 25%
ABT-594 25 mcg BID	↓ 14%
ABT-594 75 mcg BID	↓ 28%



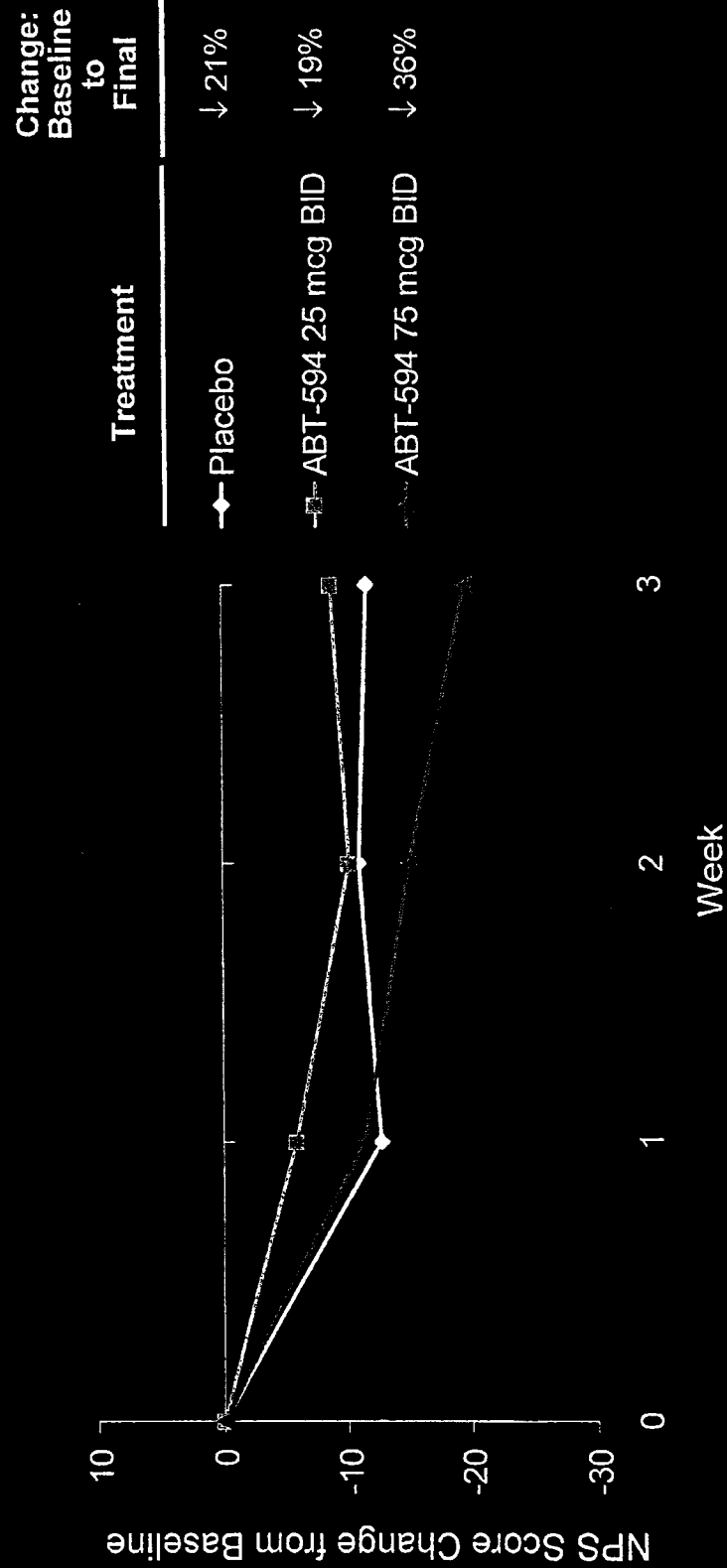
Maximum possible decrease for 75 mcg BID was 2.5

Model based, ITT  
LOCF  
833

HIGHLY  
CONFIDENTIAL

ABBT 0002414

# ABT-594 75 mcg BID Reduces the NPS More Than Placebo



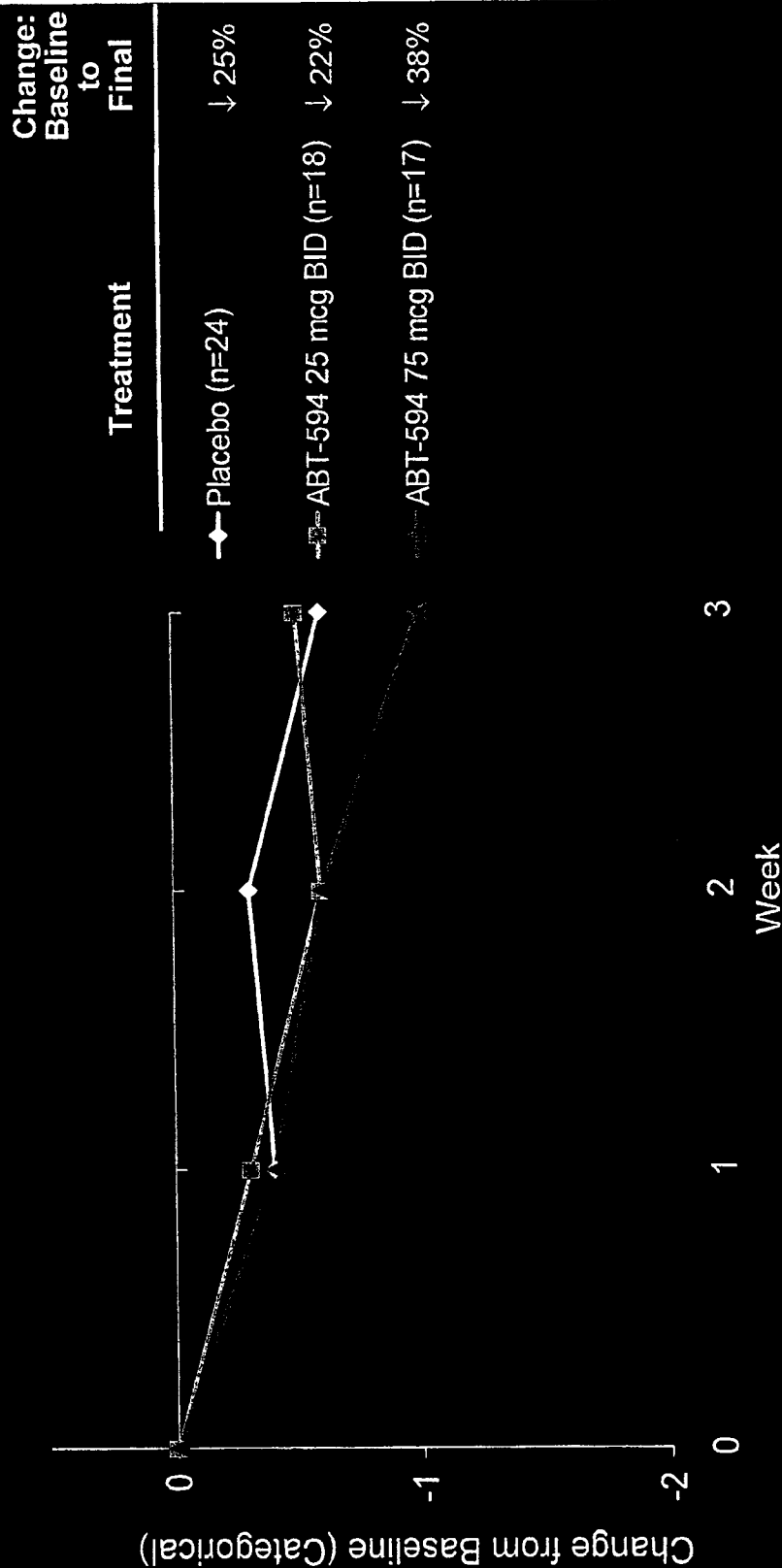
Maximum possible decrease for 75 mcg BID was 59

Model Based, ITT  
LOCF  
833

HIGHLY  
CONFIDENTIAL

ABBT 0002416

# ABT-594 75 mcg BID Reduces Daily Pain Score More Than Placebo in Diabetic Polyneuropathy



Maximum possible decrease for 75 mcg BID was 2.6

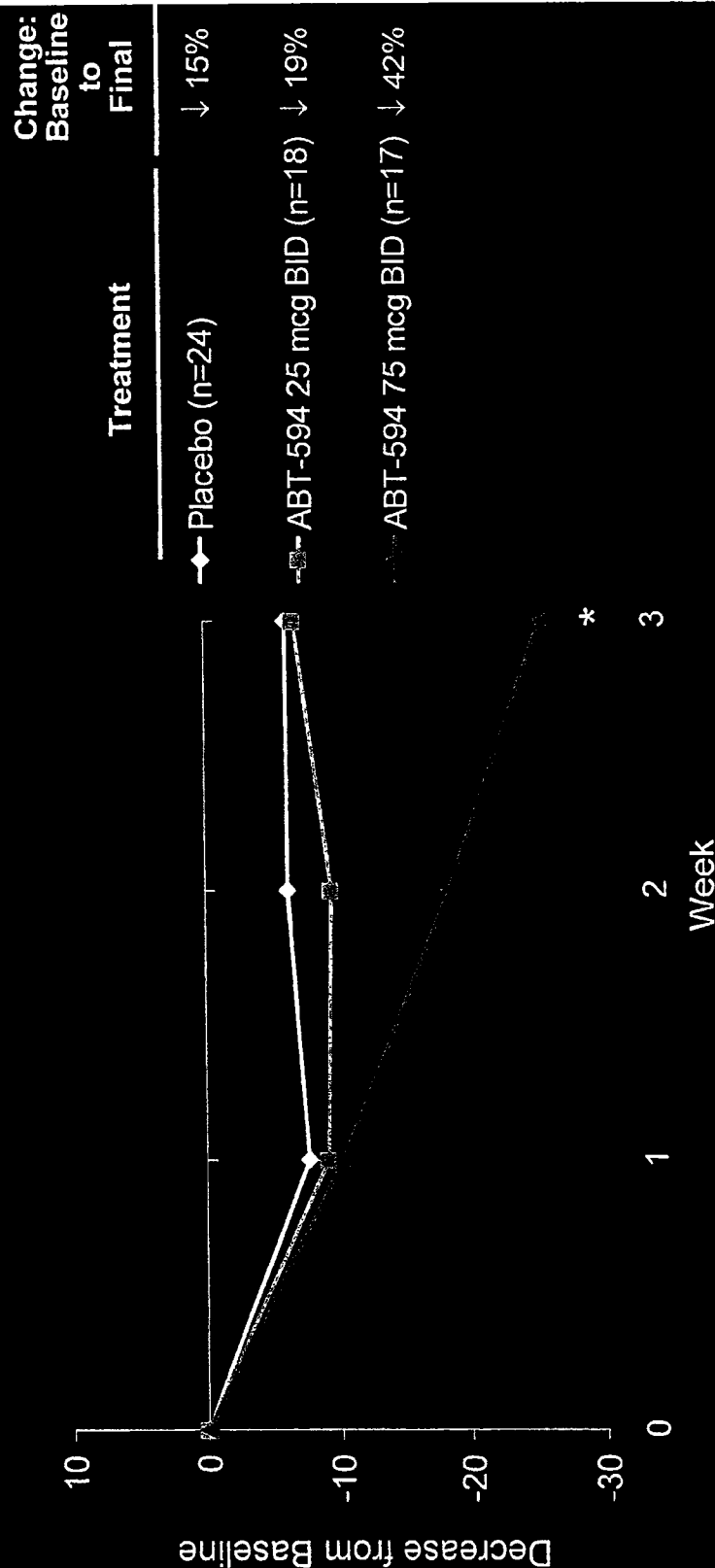
Model based, ITT  
LOCF  
833

HIGHLY  
CONFIDENTIAL

ABBT 0002416



# ABT-594 75 mcg BID Significantly Reduces NPS Compared to Placebo in Diabetic Polyneuropathy

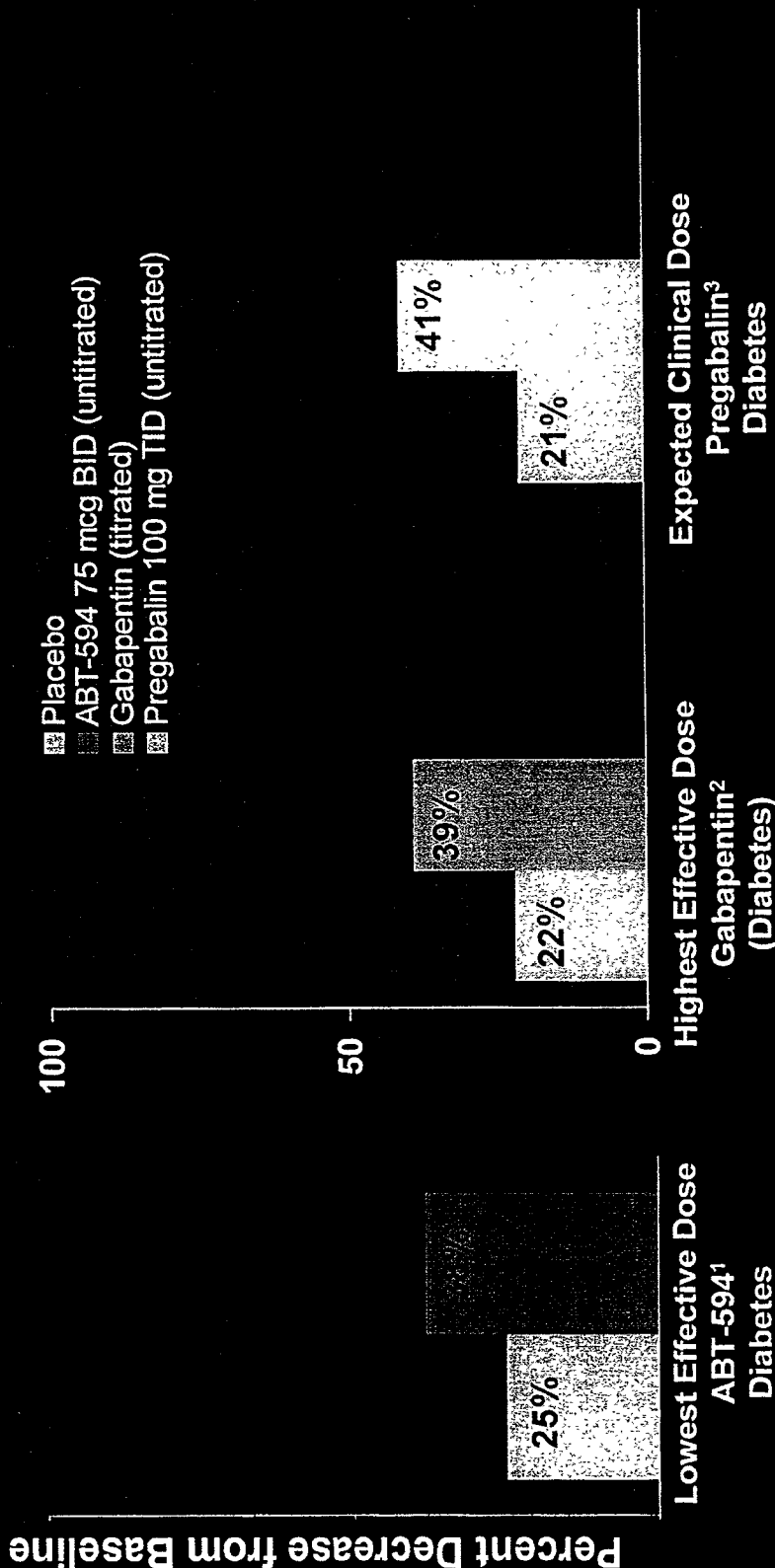


Model Based, ITT  
LOCF  
833

\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 52

# ABT-594 75 mcg BID has a Similar Effect To Gabapentin

## ABT-594 vs. Gabapentin and Pregabalin

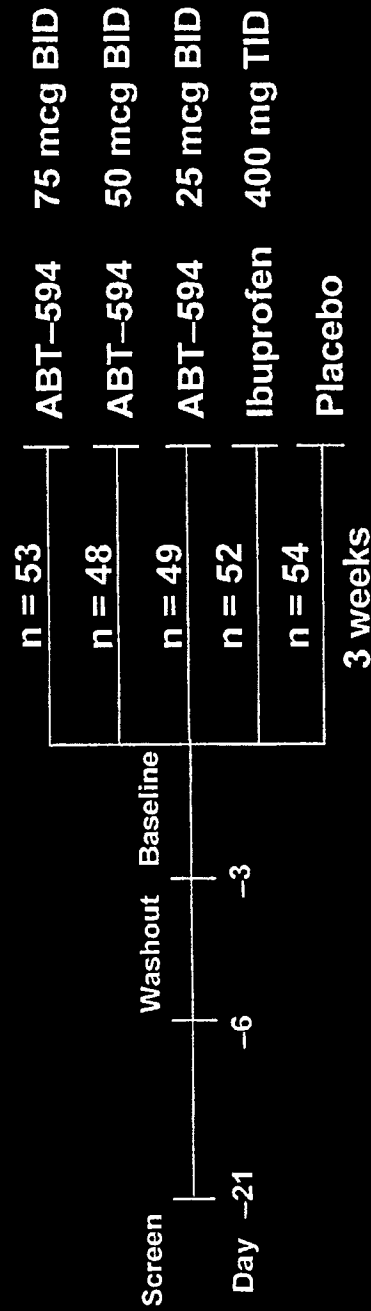


<sup>1</sup> 4-point categorical scale final vs. baseline  
<sup>2</sup> 11-point Likert Scale week 8 vs. baseline  
<sup>3</sup> 11-point Likert scale week 5 vs. baseline

# Osteoarthritis Pain Pilot

## Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

HIGHLY  
CONFIDENTIAL

ABBT 0002419

# Osteoarthritis Pain Pilot Study

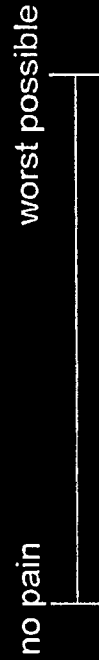
## Outcome Measures

- **Pain Intensity (PI)**

- Categorical Scale:

0	1	2	3
none	mild	moderate	severe

- Visual Analog Scale (VAS):



- **WOMAC**

- Pain (0-500)
  - Stiffness (0-200)
  - Function (0-1700)

} Total (0-2400)

- **Patient Global**

- Rate Medication:

1	2	3	4
poor	fair	good	excellent

# Osteoarthritis Pain Pilot Study

## WOMAC

### Pain

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain |

| extreme  
pain

### Stiffness

How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness |

| extreme stiffness

### Function

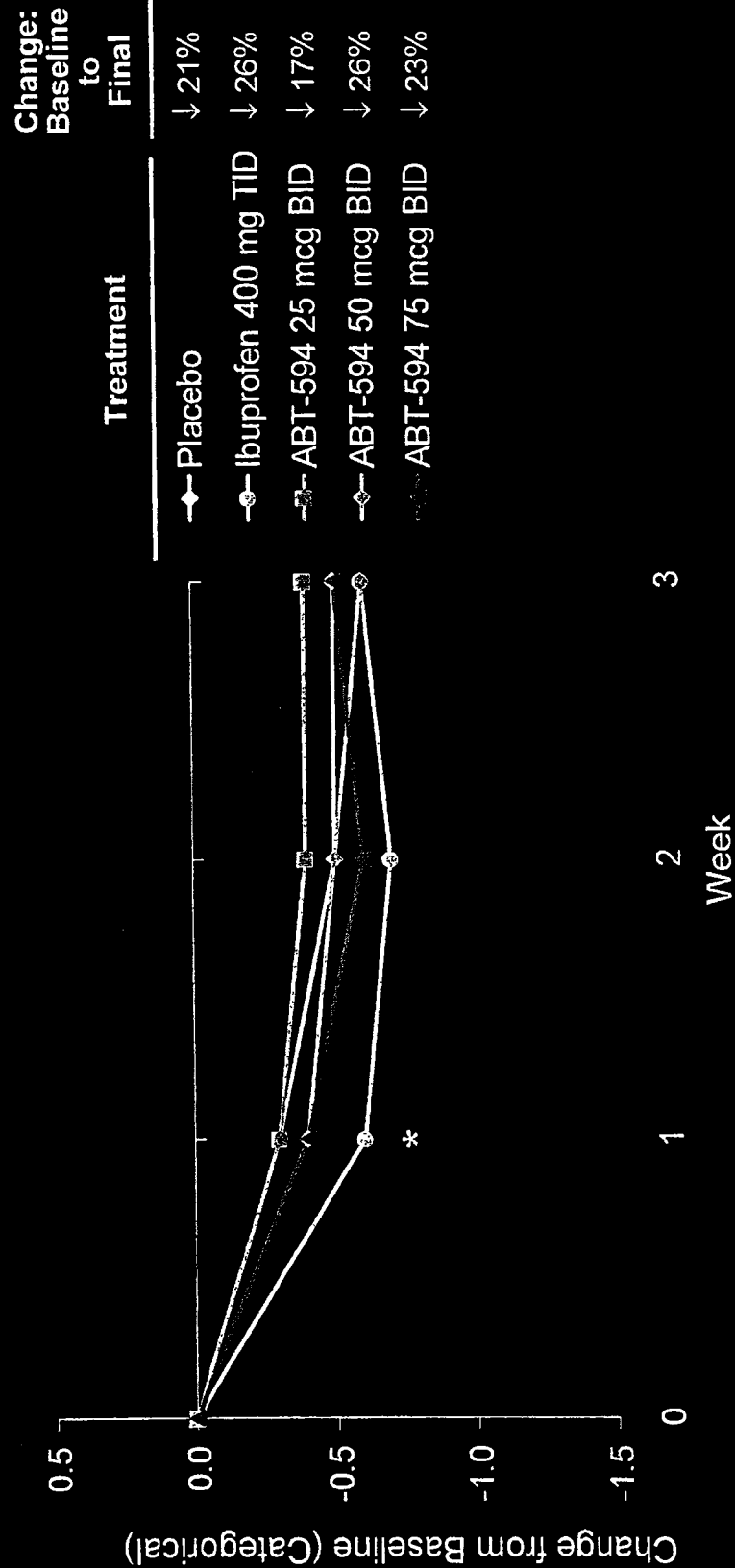
What degree of difficulty do you have...

- Descending stairs?
- Rising from bed?

no difficulty |

| extreme difficulty

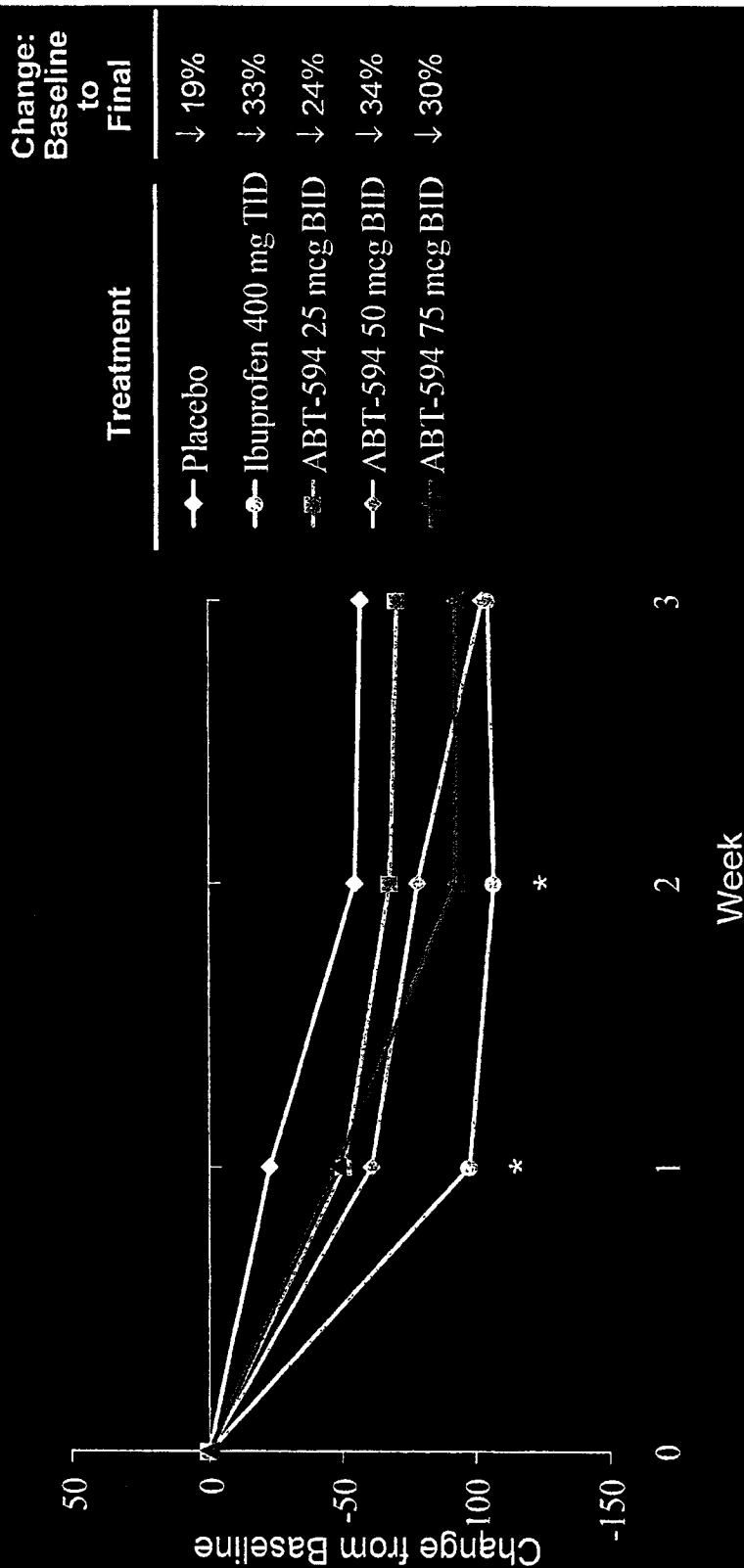
# **ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared To Placebo in Osteoarthritis**



Model based, ITT  
LOCF  
826

\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 2.2

# ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis



\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 305

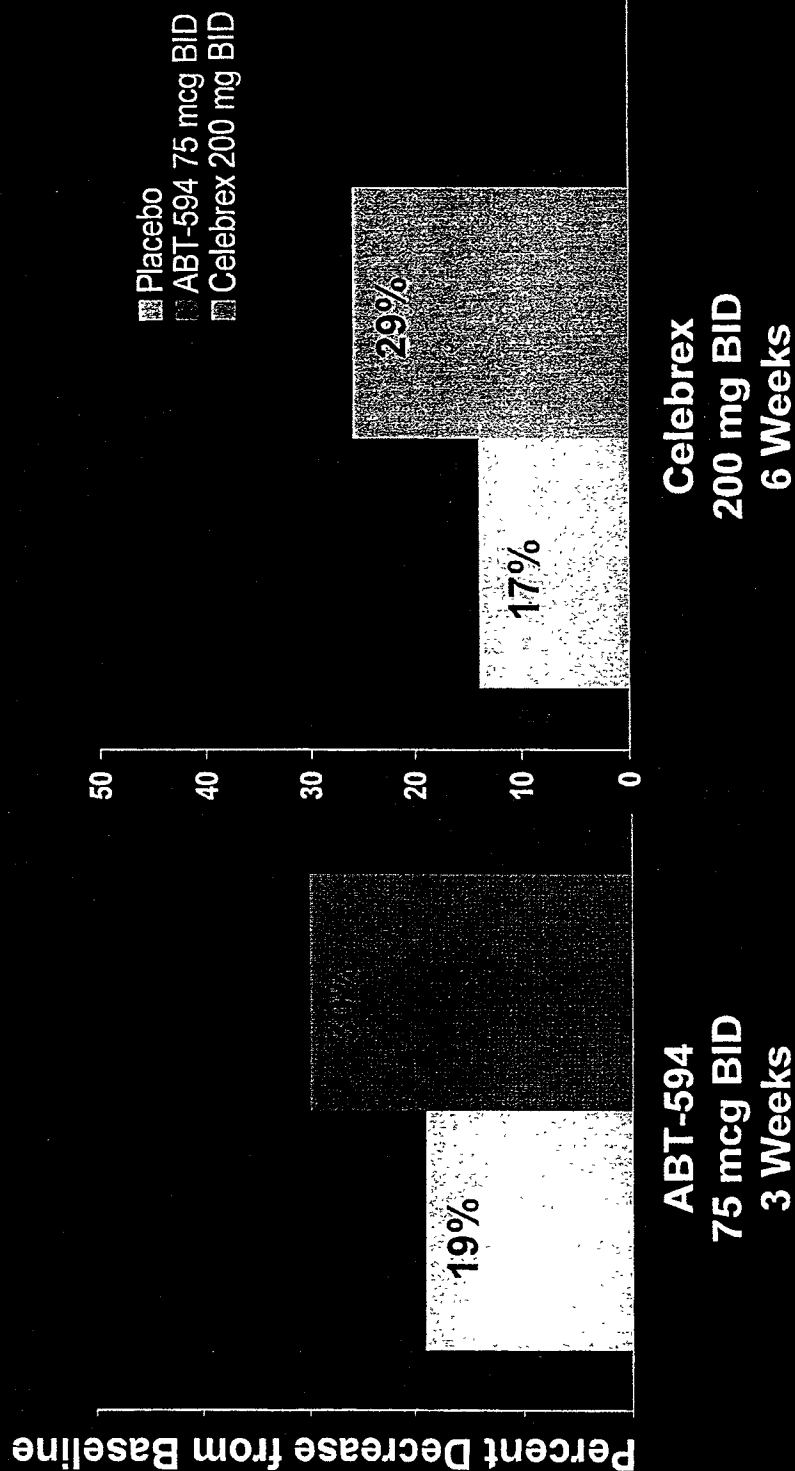
Based on 5-item (0-500 points)

HIGHLY  
CONFIDENTIAL

ABBT 0002423

# ABT-594 75 mcg BID Has An Effect Similar to Celebrex

*WOMAC Pain Decrease from Baseline*



HIGHLY  
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ABBT 0002424



# ABT-594

## *Phase IIa Efficacy Conclusions*

- Analgesic Potential Demonstrated
  - Molar Extraction
    - Significance vs. placebo starting at 1.5 hours
  - Neuropathic Pain
    - 75 mcg BID may be lowest effective dose for patients with painful diabetic polyneuropathy
  - Osteoarthritis Pain
    - 75 mcg BID may be lowest effective dose as judged by the WOMAC pain sub-score

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ABBT 0002426

# ABT-594 Safety

## *Phase IIa Adverse Events*

- Characteristic AEs
  - Nausea
  - Vomiting
  - Dizziness
- AEs attenuate after repeated administration

# Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	N/A

<sup>1</sup> Max, 1987 (n=29)

<sup>2</sup> M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002427

# Adverse Event Rates for Select Analgesics

Event	Ultram <sup>1</sup> 50-100 mg q4-6h	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12h	ABT-594 <sup>3</sup> 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

<sup>3</sup> M98-826 and M98-833 combined

N/A - Not Available

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# ABT-594

## *Phase IIa Conclusions*

- Analgesic potential demonstrated
- Phase IIa studies included inadequate dose ranging
  - SEC tolerated better than predicted by solution
  - 75 mcg BID (HGC) very well tolerated vs. other analgesics
  - Two Phase I studies (M99-076 and M99-120) showed:
    - 300 mcg BID HGC tolerated
    - Titration may improve tolerability
- Full analgesic potential should be defined with adequate dose ranging studies in Phase IIb

## Phase IIb

- Trials
  - Neuropathic Pain (M99-114)
    - Ongoing
  - Osteoarthritis Pain (M99-115)
    - Unfunded
- Doses
  - 150, 225, 300 mcg BID

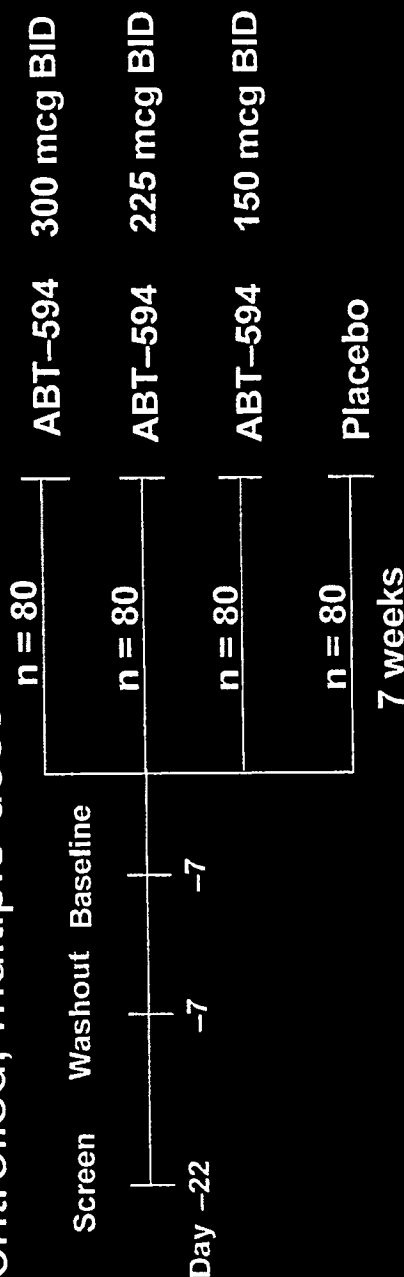
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ABBT 0002430

# M99-114: Neuropathic Pain

## Design

- 320 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-Day primer phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I to detect 39% ABT-594 improvement, 25% placebo (ES 0.46)
- Hard Gelatin Capsule

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# M99-114: Neuropathic Pain

## *Outcome Measures*

- **Primary**
  - Weekly average of daily pain (11-point Likert in a diary)
- **Secondary**
  - Site-based pain scale (11-point Likert)
  - Neuropathic Pain Scale
  - Patient Global Impression of Change
  - Physician Global Impression of Change
  - SF-36



## M99-114 Status

- Enrollment
  - Ended 1/5/01 at 269 subjects
  - Pre-specified power not reached
  - Width of confidence intervals not meaningfully different between 269 and 320 enrolled
- Database release – 5/01
- Go/No Go – 6/01

# ABT-594

## *Take Home Messages*

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
  - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

**ABT-594 Project Review  
February 2, 2001  
Commercial Assessment**

**Andrea Landsberg**

**Laura Robinson**

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**ABBT 0002435**

# **ABT-594 Commercial Assessment: Key Take Aways**

- Neuropathic pain market is the primary target
  - Underserved market with significant unmet need
  - ABT-594 has potential to be first novel drug in decades indicated for neuropathic pain
- Additional opportunity in “chronic persistent pain” market
- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*

# Neuropathic Pain Market: Sales

	2000 US Sales (\$MM)	2000 ex-US Sales
AEDs	\$299	\$190
TCAs	\$3	\$45
OPIOIDS	\$37	NA
OTHERS	\$85	\$45
<b>TOTAL</b>	<b>\$424</b>	<b>\$280</b>

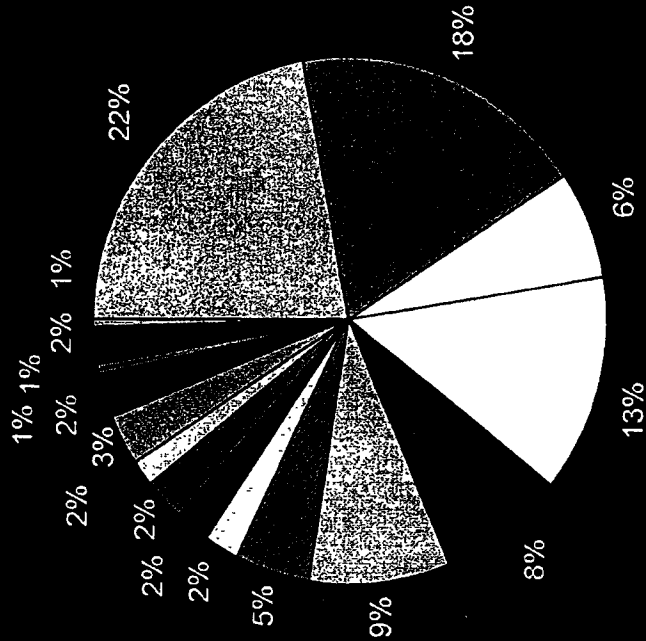
US Sales factored for neuropathic pain and annualized  
Vs Prior Year: US Growth est 20%, ex-US growth est 10%

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# Drug Classes Used to Treat Neuropathic Pain

*Dispersed market due to limited promotion and lack of dominant effective product*



**Drug Uses Data (not Rx or \$'s)**

SEIZURE DISORDERS
ANTIARTHRCS SYS PLN
COX-2 INHIBITORS
CODEINE & COMB NON-INJ
CORTICOIDS PLAIN INJ
ANTIDEP TRI/TETRA
PTY ANALGESICS
PYRIDOXINE (VIT B6)
SYN NON-NARC NON-INJ
MUSC RLX W/O ANALG
CORTICOIDS PLAIN ORAL
PROPOXYPHENES
ANESTH INJECT LOCAL
ASPIRIN,APC,ETC
SSRI'S/SNRI'S
ACETAMINOPHEN
BENZODIAZEPINES

## Use in Neuropathic Pain

- Even if target only ‘focused’ indication in ‘painful, diabetic neuropathy’ expect trial and usage in all types of neuropathic pain
  - Neurontin use all off-label
  - Carbamazepine is indicated for trigeminal neuralgia but used in all neuropathic pain
  - Generally held premise that NP likely has some similar mechanisms across etiologies (reinforced by current drug usage)

# Market Opportunities in Neuropathic Pain

- Improved efficacy
  - Partial pain relief is the norm
  - Polypharmacy often required to manage pain
- Improved responder rates
  - Typically only 40% to 60% of patients respond to any given treatment
- Improved tolerability over time
  - TCAs, AEDs, opioids have troublesome SEs that do not diminish over time
- Dose reduction
  - Most TCAs and AEDs (including Neurontin) typically dosed TID
- Titration reduction
  - TCAs and AEDs require >2 weeks titration period to minimize SEs or reach effective dose

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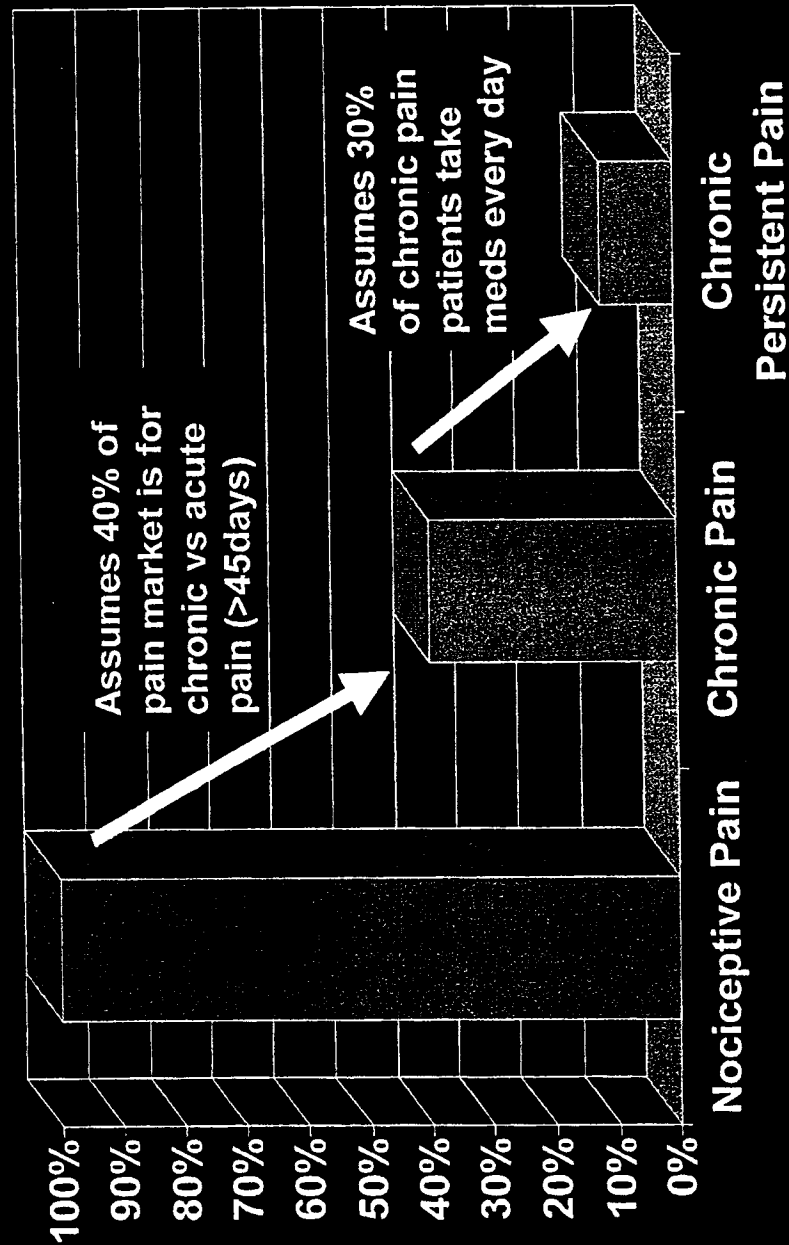
# Chronic Persistent Pain (CPP) “Spillover”

- Onset of action and need for titration limits ABT-594 to a small segment of the nociceptive pain market
- CPP = Chronic persistent pain conditions for which patients are on daily medications, over extended periods of time (vs. PRN, or ‘as needed’, consumption)

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# Chronic Persistent Pain



IMS Longitudinal Data indicates over 80% of pain meds Rxed for >=30 days  
Quantitative primary market research indicates that >60% of chronic pain patients take meds every day

# Chronic Persistent Pain Market

	1999 Sales (\$MM)	CAGR (97-99)	Rxs (MM)	CAGR (97-99)
US	\$700	5%	35	1%
Ex-US	\$680	8%	58	3%

CPP Market Size Assumptions:  
 Assume 40% of opioid, non-opioid, COX-2 market is for chronic pain and  
 30% of that is 'persistent', i.e.: medication taken every day

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ABBT 0002443

# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back

*Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain*

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ABBT 0002444

# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent			
Same	Equivalent			
Better	Poor			

TCAs used as "benchmark" efficacy in NP

Tolerability vs. current agents: equivalent = 5% nausea; 5% vomiting; 10% dizziness; poor = 20% nausea; 10% vomiting; 30% dizziness

# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent	19%	12%	16%
Same	Equivalent	15%	8%	10%
Better	Poor	12%	6%	11%

*Spillover market share in chronic persistent pain markets (in forecast, assuming only 5% share)*

*MR did not test impact of titration on market share*

# Qualitative Market Research Results

Profile		Share of Patients
Efficacy	AEs vs. current agents	Neuropathic Pain
Better	Equivalent	31%
Better	Poor	24%
Same	Equivalent	27%

*Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain*

*In forecast assuming 20% share of NP*

# Neuropathic Pain Pipeline

- Pregabalin is in Phase III, but questions remain regarding Pfizer's Neurontin/Pregabalin strategy
- 4 NNR preclinical programs appear to be targeting pain indications; ABT-594 is much further along
- Other new AEDs may have potential for treatment of neuropathic pain and are conducting phase IV trials; unclear whether these agents will pursue an NP indication
- Several novel pain mechanisms being explored
  - Calcium channel blockers
  - Sodium channel blockers
  - NMDA antagonists



## Positioning of ABT-594 in Neuropathic Pain

- Greater efficacy than AEDs and TCAs in NP
- Better long term tolerability (than TCAs and opioids)
- Safe in all patient populations
- Convenient BID dosing with simple, short titration period
- No tolerance over time and non-scheduled
- Limited drug interactions
- Novel mechanism of action

# Positioning of ABT-594 in CPP

- Effective alternative to opioids with:
  - No tolerance, respiratory depression, constipation, etc.
  - Non-scheduled
- For patients receiving insufficient relief with current therapies or NSAID/opioid intolerant patients
- Better efficacy than COX-2s with novel mechanism of action and no major safety issues

# ABT-594 Global Forecast Ranges

(\$MM)

	Peak Sales		
	Low	Base	High
US	\$92	\$339	\$509
Ex-US	\$130	\$363	\$712

- NP shares: 5%, 20% or 30%
- CPP shares: 3%, 5%, 7%

# Key Product Challenges

- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*
  - Neurontin/Pregabalin may have advantage
    - Will need to minimize early DCs as much as possible
  - Potentially low therapeutic index
- **Titration**
  - Schedule must be as short and simple as possible
- **Nicotinic mechanism**
  - Will require pre-launch market education and priming to diffuse negative associations and generate interest surrounding novel MOA

**Go/No Go Process**

**Bruce McCarthy**

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**ABBT 0002463**

# ABT-594

## *Go/No Go Process*

### The Challenge

Integration of many interrelated data

Efficacy

Safety

Dose Response

Pharmacodynamics

Dose Selection

Phase III Trial Design

Titration Effects

Indications

Market Research

Segmentation

Targeting

Positioning

### The Plan

Leverage decision analysis (DSG) as a process  
to determine Go/No Go criteria

# ABT-594

## *Go/No Go Process*

### **Process to include:**

1. Scope and frame issues and process
2. Analysis of M99-114 and other clinical data
3. Dose identification
4. Draft Phase III trial design
5. Market research
6. Valuation
7. Presentation and asset strategy: 6/01

Decision Analysis

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# ABT-594

## *Go/No Go Process*

**What will a “Go” decision look like?**

Patients and physicians will have  
compelling reasons to choose ABT-594 vs.  
other analgesics for the relief of pain



# **ABT-594 Project Review February 2, 2001**

## **Follow-On Strategy**

**Mike Meyer**

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**ABBT 0002467**

# Identification of ABT-594 Backup

## *Clinical Results Outline Specific Improvements Required for Backup*

- Emesis
  - Modeled preclinically in ferret and dog
- Nausea
  - Ferret model can qualitatively address nausea index
- Dizziness
  - Mouse rotarod
  - Rat Edge test

# Discovery Program Basis

## *NNR Subtypes Differentially Mediate Efficacy and Side Effects*

- Different NNR subtypes mediate analgesic effects of nicotinic agonists and adverse events
- Program committed to the identification of NNR subtype selective compounds
- Project initiated research collaboration with NeuroSearch (Denmark)
  - Access to human recombinant NNRs
  - Access to new structural classes of NNR modulators

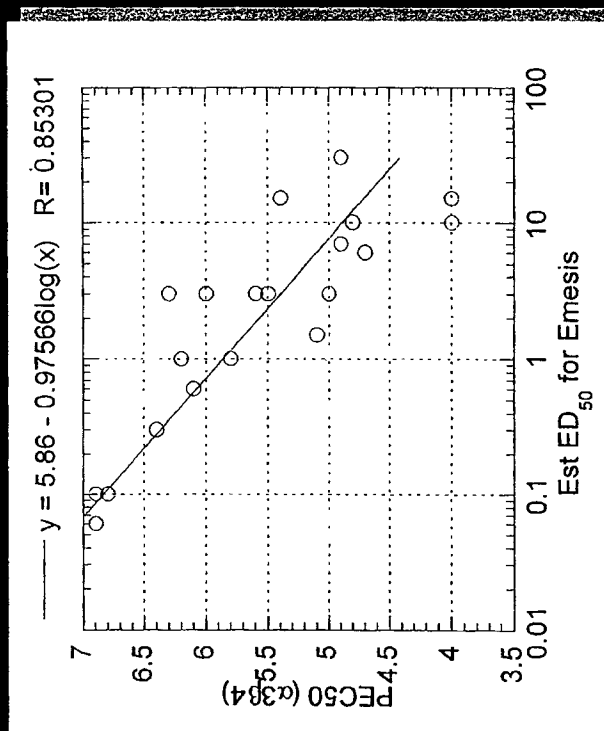
# Nociception Mediated by $\alpha 4$

## Subtypes

- Mouse knockouts support role of  $\alpha 4$  and  $\beta 2$ 
  - Key differences between pain type
- Role for  $\alpha 4$  subtype in acute thermal pain (activation of descending inhibitory pathways)
  - Antisense studies
  - Site injection studies
  - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

# Emesis Mediated by $\alpha 3\beta 4$ Subtype

- In preclinical models, emesis is correlated to potency and efficacy at ganglionic ( $\alpha 3\beta 4$ ) NNR subtypes
- Antagonist and route of administration studies suggest both local and systemic contribution



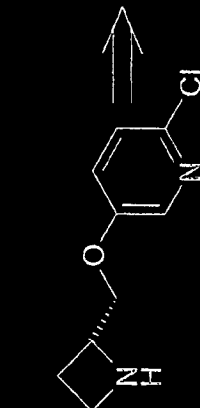
# $\alpha$ 4-Selective Ligands: In Vitro Profile

## • Radioligand Binding Profile:

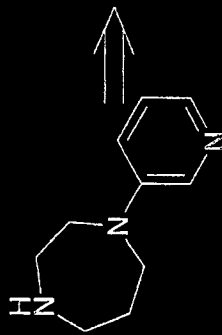
0.046 nM

0.049 nM

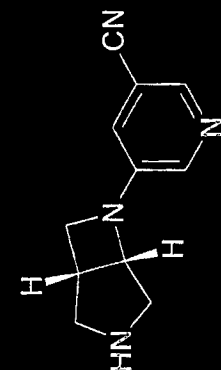
3.19 nM



ABT-594

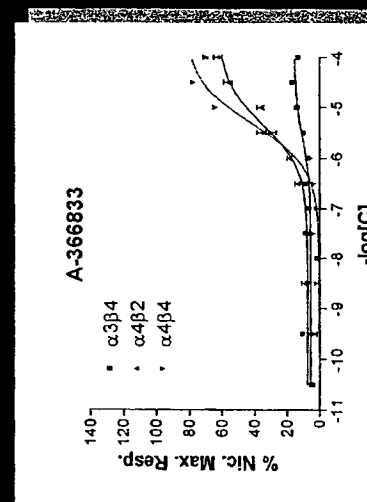
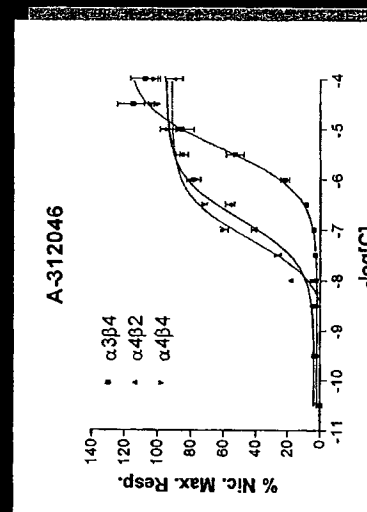
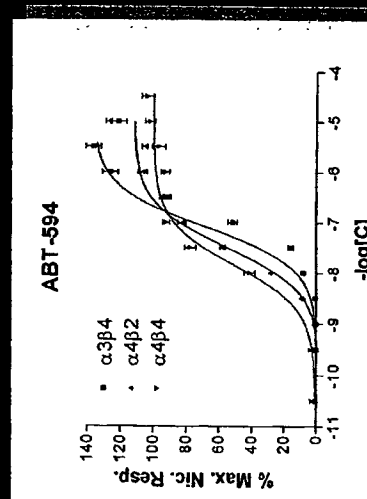


A-312046



A-366833

## • In Vitro Functional Profile:



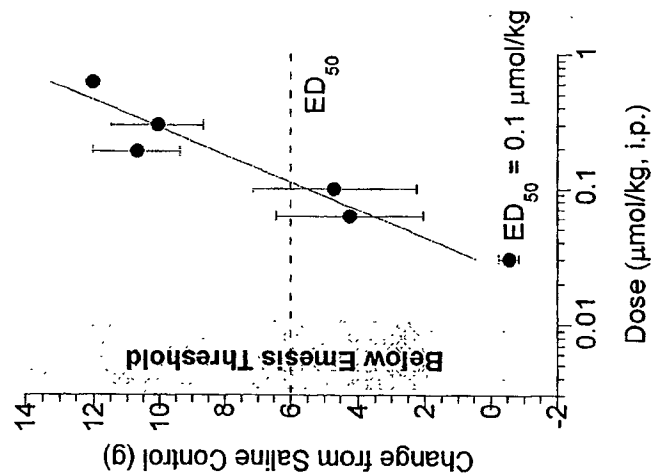
# Analgesic Efficacy vs. ABT-594 (Rat Models)

	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 $\mu$ mol/kg)	+++ (0.1 $\mu$ mol/kg)	+++ (0.03 $\mu$ mol/kg)
A-312046	+++ (1.8 $\mu$ mol/kg)	+++ (0.7 $\mu$ mol/kg)	+++ (1.9 $\mu$ mol/kg)
A-366833	+++ (3 $\mu$ mol/kg)	+++ (5 $\mu$ mol/kg)	++ (6 $\mu$ mol/kg)
Celecoxib	++ (30 $\mu$ mol/kg)	+	0
Morphine	+++ (3 $\mu$ mol/kg)	+++ (10 $\mu$ mol/kg)	++ (3 $\mu$ mol/kg)
Gabapentin	+	++ (100 $\mu$ mol/kg)	0

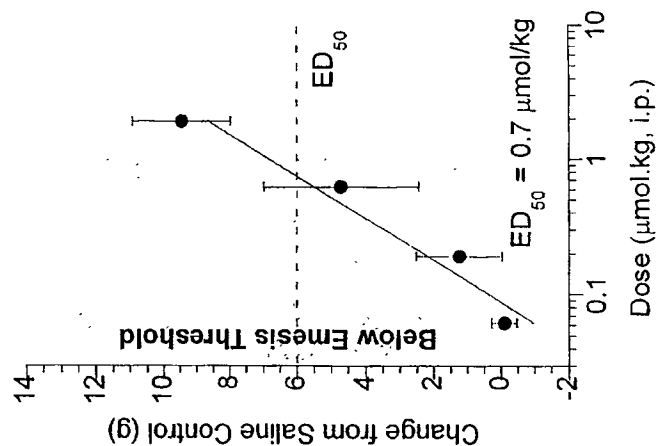
+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

# Efficacy Indexed to Emesis Liability (Neuropathic Pain)

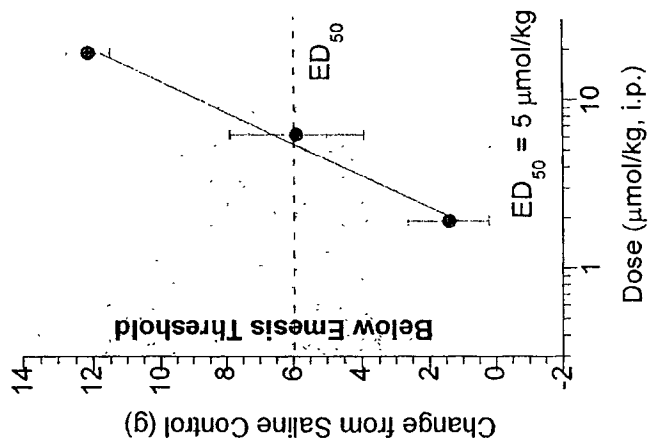
ABT-594



A-312046

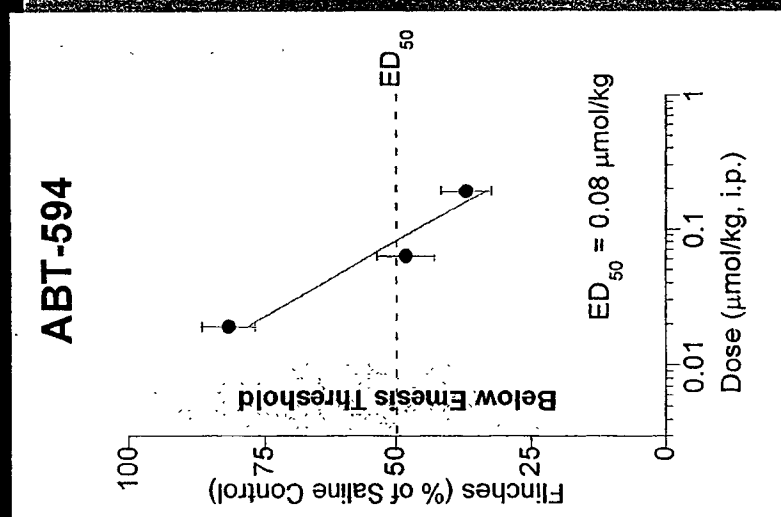
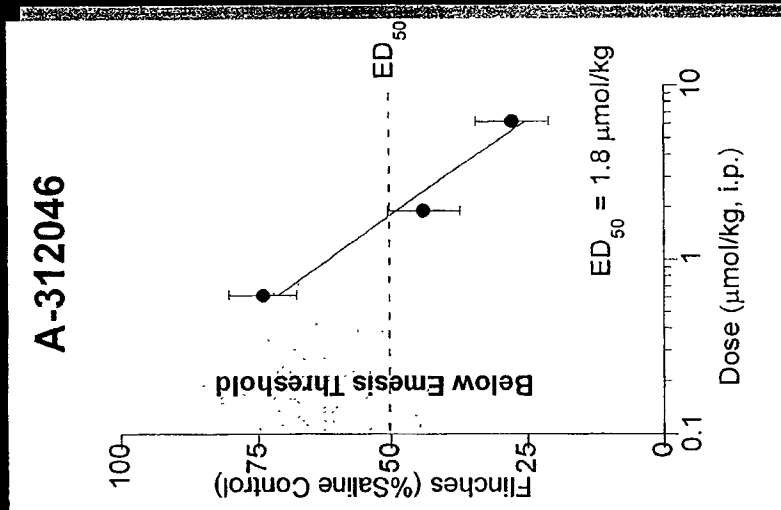
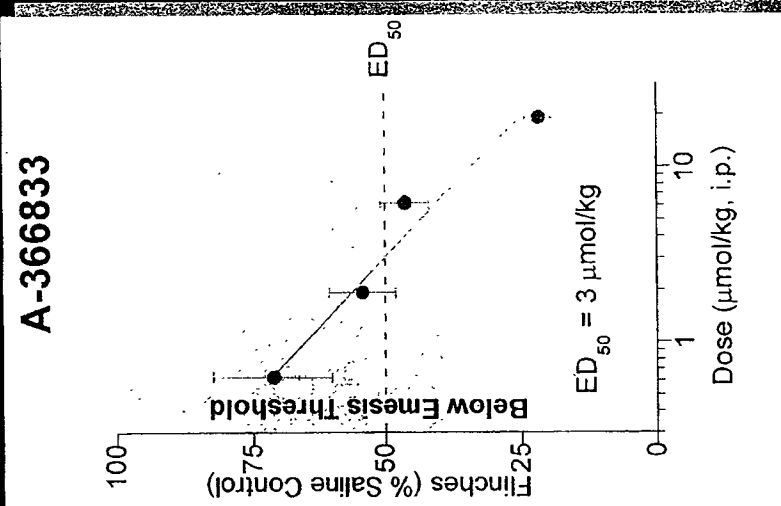


A-366833





# Efficacy Indexed to Emesis Liability (Nociceptive Pain)



HIGHLY  
CONFIDENTIAL

ABBT 0002466

# Therapeutic Index Comparison

- Therapeutic index based on ratio of highest no effect dose for adverse event and ED<sub>50</sub> in pain models

Adverse Event	Therapeutic Index Improvement vs. ABT-594	
	A-312046	A-366833
Emesis (Ferret)	5 - 14x	20 - 27x
Seizure Threshold (Mouse)	4 - 11x	>11x
Edge Test (Rat)	7 - 24x	>12x

# Pharmacokinetics

	$t_{1/2}$	CLp	%F
Rat	1.5 h	1.7	61%
Dog	4.7 h	0.4	35%
Monkey	1.4 h	1.7	80%
Rat	3.0 h	1.95	80%
Dog	1.4 h	2.89	13%
Monkey	1.5 h	2.36	3%
Rat	1.5 h	3.02	73%
Dog	2.6 h	0.35	109%
Monkey	2.5 h	0.53	74%

ABT-594

A-312046

A-366833

## Additional Characterization and Ongoing Studies

- A-312046:
  - Evaluation of viability of transdermal formulation
  - Identification of prodrug analogs
- A-366833:
  - Ames and chromosomal breakage neg.
  - CEREP binding studies – no significant findings
  - Ongoing studies:
    - Evaluation in additional pain models
    - PK/PD studies – plasma levels at efficacious and emetic doses
    - Dog, monkey, human hepatocyte metabolism
    - Cardiovascular evaluation
    - Two-week toxicology in rats

## Backup Status

### • A-366833:

- Broad spectrum activity, but particularly effective in persistent nociceptive pain model
- Significantly decreased side effect liability
- Excellent oral bioavailability across three species
- May extend into general pain indication

### • A-312046:

- Excellent activity in neuropathic pain model
- Pharmacokinetics may preclude development as oral drug
- Alternative formulations may be useful as backup for ABT-594 in neuropathic pain market





From: Jeff Leiden  
John Leonard

**INTEROFFICE CORRESPONDENCE**

---

TO: Miles White

Date: Jan. 7, 2002

CC:

Bill Dempsey  
Dave Goffredo  
Mary Szela  
Jim Tyree  
Eugene Sun  
Stan Bukofzer

**Confidential**

**RE:**

On December 10<sup>th</sup>, the Pharmaceutical Executive Committee met to review the development status of ABT-773, our ketolide antibiotic in clinical development for respiratory tract infections. Based on the data reviewed at the meeting, the Committee recommends suspending further development and initiating efforts to out license the compound. Attached is a package, which addresses the key issues. Our decision for this recommendation is based on the following:

**1. Divergence from the target product profile**

ABT-773 was approved for clinical development in a March 1997 Drug Development Committee (PPCC), at which time the key elements of the target product profile were defined as:

- ◆ Once daily dosing for short course treatment regimens (5-10 days)
- ◆ Favorable side effect profile relative to currently available therapies
- ◆ Efficacy against major respiratory pathogens, particularly against resistant organisms, a key differentiating feature of this compound
- ◆ Once daily dosing has not been achieved in 3 of 4 respiratory indications:
  - ◆ In July 2001, twice daily dosing was chosen for the pivotal Phase III clinical trials in sinusitis and community acquired pneumonia. This decision was taken based on accumulated scientific data and to enhance regulatory approvability of the compound, but recognized a corresponding decrease in the commercial value; particularly given the global trend toward once-a-day/shorter course therapy.
  - ◆ In November, the pivotal U.S. Phase III trial in pharyngitis showed that ABT-773 dosed once daily at the chosen dose had insufficient efficacy for approval. Additionally, these results cast some doubt on the potential for QD dosing for bronchitis.

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ABBT0559668

- ◆ The emerging side effect profile of ABT-773 is neither significantly better nor worse than clarithromycin in terms of taste and the potential for drug-drug interactions. There are still safety issues that remain to be better defined, i.e., the potential for QT prolongation, and the incidence and severity of liver enzyme abnormalities (see #3 below).
- ◆ A resistance claim, which is a key point of commercial differentiation, will be challenging to achieve:
  - ◆ The resistance claim is based on successful treatment of pneumonia patients who have resistant organisms. The original ABT-773 plan targeted approximately 15 such patients. In 2001, the EMEA and FDA evaluated telithromycin (Ketek), Aventis' first-in-class ketolide. Neither the EMEA nor FDA considered the Ketek data sufficient to support a resistance claim based on 17 patients with about an 85% eradication rate. It is now anticipated that a resistance claim for ABT-773 will require a larger number of resistant isolates (this requirement will significantly increase the size, complexity, and duration of clinical trials) as well as an eradication rate of at least 85%.

## 2. Increasing regulatory stringency

- ◆ Regulatory approval of new antibiotics is increasingly dependent on their benefit:risk ratio compared to currently available therapies. Given that most respiratory antibiotics have greater than 85% success rates there is increasing attention to drug safety. Although Ketek was approved by EMEA this year, significant post approval commitments were mandated, i.e., additional safety data in over 4000 patients. In the US, Aventis has been asked to obtain additional safety data prior to FDA approval. Given that some of the same safety issues may apply to ABT-773, the projected size of the required safety database for ABT-773 has increased considerably. This will increase the expense and duration of the phase III trials.
- ◆ Regulatory authorities are increasingly concerned about widespread antibiotic resistance resulting from inappropriate antibiotic usage. They are considering ways to curb indiscriminate antibiotic usage, such as limiting regulatory approval for indications that do not always warrant antibiotic therapy, e.g., acute exacerbation of chronic bronchitis. This indication represents one of the largest respiratory market segments.

## 3. Unresolved potential safety issues

- ◆ QT prolongation by ABT-773 has not been fully characterized and remains a potential liability. In recent years, broad regulatory attention to this issue has resulted in increasing requirements for *in vitro* as well as clinical data to assess this risk. To date, data indicates that QT prolongation by ABT-773 is comparable to that of clarithromycin and Ketek, but FDA has requested additional studies. Should these studies suggest clinically significant risk, regulatory actions could include non-approval, Black Box warning, or contraindication in at-risk populations.



- ◆ Significant liver enzyme elevations have been observed in a few subjects in clinical trials to date, most recently in a study to evaluate QT prolongation. Clinical protocols have been modified to increase patient monitoring, leading to increased clinical costs and a delay in filing. Although the incidence and severity of these findings fall within an acceptable range for antibiotics, future findings may drive the requirement for a larger safety database.

#### **4. Decreased commercial valuation**

- ◆ The loss of the pharyngitis indication is forecasted to erode more than \$117MM in NPV from ABT-773 (-\$82MM AI; -\$35MM PPD). Based on the above information, the global NPV of ABT-773 falls from a July 2001 \$223MM to \$51MM with the U.S. market NPV largely break-even at \$3MM and Abbott International contributing the balance of value.
- ◆ In addition, if the regulatory authorities require additional patients to evaluate safety, the value of ABT-773 becomes negative.

Attached are several slides that provide additional detail to the issues discussed above. Obviously we are extremely disappointed to recommend stopping a key phase III program in development. However, at this time, the team recommends placing development on hold and redirecting R & D funds to higher return opportunities. If this decision is made shortly, the team forecasts that it would create a 2002 R&D favorability of approximately \$47MM.

#### **Next Steps**

We look forward to meet with you regarding our recommendation and to secure your approval to move forward with the decision to place clinical development on hold. If approved, the next steps will include:

- ◆ The preparation of an internal and external communication package for all stakeholders paying particular attention to PR issues and timing of the process.
- ◆ Communicating with Taisho. As you are aware, the development of ABT-773 has been conducted in collaboration with Taisho under a 1997 Agreement in which Taisho contributes 50% of the Japanese development cost and 10.69% of the ex-Japan expenses. Abbott has the right to out license the compound outside Japan without Taisho's consent, but the royalty obligations remain in effect (5.5% in patented territories and 2.75% in non-patented countries). Sub-licensing of Abbott's rights in Japan is allowed only after Taisho's consent.
- ◆ The PEC believes that the compound may hold potential for out licensing. To capture value for ABT-773 an out licensing effort, which might include follow-on compounds already in discovery, would be aggressively initiated.



# Abbott Portfolio Review

March 7-9, 2001

- Project ABT-518
- Compound Matrix Metalloproteinase Inhibitor
- Presenter Perry Nisen
- Project Team Members

A. Nabulsi (VH), T. Janus (MD), D. D'Amico (CPM)

## ABT-518

- ◆ Target indication: Solid tumors
- ◆ Targeted unmet medical need: Cancer
- ◆ Target product profile vs. current gold standard:

## ABT-518

### ◆Key pre-clinical findings:

#### - Pharmacology

- Potent and highly selective (gel-A and gel-B) MMP inhibitor
- Anti-tumor activity seen in numerous murine cancer models
- Inhibition of tumor growth is dose dependent
- Blocks vessel formation in a mouse model of angiogenesis

#### - Pharmacokinetics / Metabolism in animals

- Sustained plasma concentrations following single-dose in monkeys
- Oral bioavailability between 68 and 93% in animals
- Multiple metabolites are produced after repeat dosing in rats and dogs

#### - Toxicology

- No meaningful effects in genotoxicity, cytotoxicity or ligand binding assays
- No remarkable cardiovascular effects in dogs
- Steatosis seen in high-dose rats two weeks after drug stopped

## ABT-518

### ◆Chemistry and Manufacturing

#### Drug substance

- Six steps from commercial starting materials
- 3-month turnaround time to manufacture
- Manufactured at Abbott

#### Drug product

- Neat drug in a capsule (25 and 200 mg) for Phase I
- Hand-fill or semi-automation at a third party manufacturing facility (Phase I)
- Formulation development work will begin post Phase II Go/No Go decision

## ABT-518

### ◆ Global clinical development plan

Approval ◆

File NDA ◆



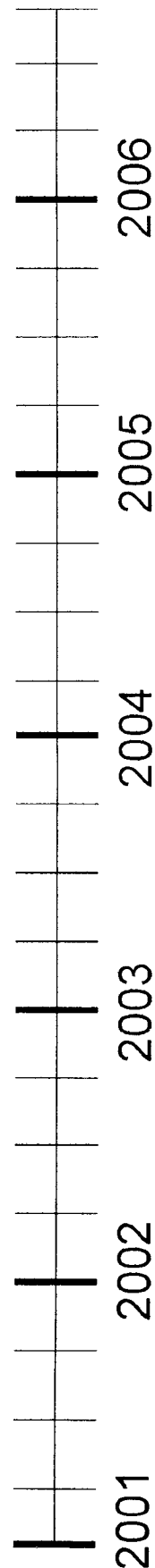
Phase III



Phase II



Phase I



## ABT-518

### ◆Clinical development budget

Phase	Funding (\$MM)
Pre-Clinical	5
Phase I	12
Phase II	47
Phase III	78



## ABT-518

### ◆Phase I study:

#### Multiple-dose study in patients with advanced cancer

- Objectives
  - Establish safety profile
  - Determine the maximum tolerated dose (MTD)
  - Assess PK
  - Determine Phase II dose
- Design
  - 28 days + extension
  - Single-dose of drug administered on Day 1; resume dosing (daily) on Day 4
  - Approximately 40 patients; 3 patients per dose
    - Add 6 or more patients at MTD to collect additional safety information
  - Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day

## ABT-518

### ◆Phase I plan:

#### IND Study

##### - Objectives

- PD-guided Phase II dose selection
- Long-term safety

##### - Design

- Multiple dose escalation study
- Assess MMP activity in accessible tumors
  - Melanoma
  - Head and Neck Cancer
- Approximately 20 patients

## ABT-518

### ◆Phase II development plans:

- 3 Studies
  - 3 Tumor types as defined by Phase I and animal efficacy
  - 150 patients per study
- Dose finding
- Assess safety issues identified in Phase I
- Thirteen month duration

## ABT-518

### ◆Phase III plan:

- Demonstrate improvement in survival or TTP in combination with cytotoxic therapies

## Strategic Summary

### ABT-518

#### ◆Key project strengths / positives:

- **Product attributes**
  - Highly selective for the inhibition of gelatinases A & B
  - Very potent
  - No joint-toxicity expected
  - Potentially best in class

#### - **Technology / Innovation**

- Oral, once-a-day dosing

#### - **Time to market**

- Potential for fast-track approval
- Launch 2Q06

#### - **Business franchise strength**

- Comprehensive oncology franchise
- Synergies with HPD and ADD

#### - **Other relevant points**

- Competitors in class
- Non-oncologic indications
  - » Multiple sclerosis
  - » Proliferative retinopathy
  - » Arthritis

## Strategic Summary

### ABT-518

#### ◆ Potential issues / Threats / Negatives:

##### – Toxicity / side effects

- Metabolites that may accumulate over time
- Potential mechanism-based drug interaction (CYP3A inducer-inhibitor)
- Microvesicular and macrovesicular steatosis in rat study

##### – Manufacturing / cost of goods – No issues anticipated

##### – Efficacy

- Data released from competitors may cast doubt on class

##### – Clinical recruitment problems

- Extensive protocol prohibited medications list

##### – Regulatory risk

- No precedent for cytostatic drug approval
- Undefined clinical endpoints
- Competitor data may pose additional development hurdles

##### – Technical risks – No issues anticipated

##### – Other relevant issue

- No good models for selection of dose, regimen and responsive tumor types
- PD marker selection

## Strategic Summary

### ABT-518

#### ◆Key decisions:

- Important upcoming decisions
  - Transition team Go/No Go Phase II - 12/01
- Proposed budget (2001, and all years to launch)

Year	R&D per year (\$MM)
2001	7
2002	38
2003	36
2004	29
2005	23
2006	8

Strategic Summary

**ABT-518**

**◆Key decisions:**

- Evaluate safety at multiple doses and dose regimens
- Dose and regimen selection for Phase II
- Tumor type selection for Phase II
- Clinical trial design to demonstrate efficacy



## Strategic Summary

### ABT-518

#### ◆ Proposed action plans

##### – **Manufacturing**

- Initiate formulation work post Phase II Go/No Go

##### – **Nonclinical**

- Additional toxicology and metabolism studies are underway to explore the CYP3A and steatosis issues

##### – **Clinical**

- Measure metabolites in Phase I
- Assess bioactivity via PD markers in Phase I
- Hold a Pre-IND meeting with the FDA to discuss endpoints

##### – **Contingency plan**

- Pursue alternative indications
  - Multiple sclerosis
  - Proliferative retinopathy
  - Arthritis



ABT-594  
Pharma Executive Management  
Committee Review

August 21, 2001

*Leiden* 32  
EXHIBIT  
FOR ID. 4-26-07-1 *gmc*

## ABT-594 August 2001 Review

- |                      |                                  |
|----------------------|----------------------------------|
| ▪ Development Update | Bruce McCarthy                   |
| ▪ DSG Analysis       | Steve Kuemmerle<br>(Liz Kowaluk) |
| ♦ NNR Follow-ons     | Michael Meyer                    |

August 17, 2001

2

### ABT-594 August 2001 Review Topics

- ABT-594 efficacy in neuropathic pain is significant
  - ABT-594 has a narrow therapeutic window and efficacious doses are poorly tolerated as dosed currently
  - Modifications to drug administration have the potential to improve tolerability
- Decision analysis suggests that the expected value for these modifications (to improve tolerability) is small, although positive
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

August 17, 2001

3

## ABT-594's Potential for Pain Relief

- Efficacy across preclinical models of pain
  - Efficacy of morphine without morphine-like adverse events
  - Efficacy in neuropathic pain
- Commercial and clinical development plan targeted acute and chronic nociceptive pain and neuropathic pain, based upon preclinical promise
- Tolerability/onset of action issues made neuropathic pain relatively more attractive
  - Dosages that provide meaningful acute relief of pain are not well tolerated
  - Titration not well suited to intermittent use, as seen with most chronic nociceptive pain
  - Titration is used with all currently available drugs for neuropathic pain

August 17, 2006

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**ABT-594 Review:**

**Diabetic Neuropathic Pain Phase IIb  
Study Results (M99-114)**

---

**August 21, 2001**

Phase IIb Study in Neuropathic Pain (M99-114)

*Study Results*

- Summary
- Neuropathic pain reminder
- Study Design
- Efficacy Results
- Adverse Events
- Conclusions and Options

August 17, 2001

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### Phase IIb Study in Neuropathic Pain (M99-114)

#### *Summary*

- EFFICACY

- 150, 225 and 300 mcg BID are significantly better than placebo as measured by the primary efficacy variable (reduction in daily pain)

- ITT Analysis: 29-30% vs. 17% placebo
  - Gabapentin: 39% vs. 22% placebo
- Completer Analysis: 38-48% vs. 18% placebo
- Responder rates: 26% (ITT), 47% (Completer)

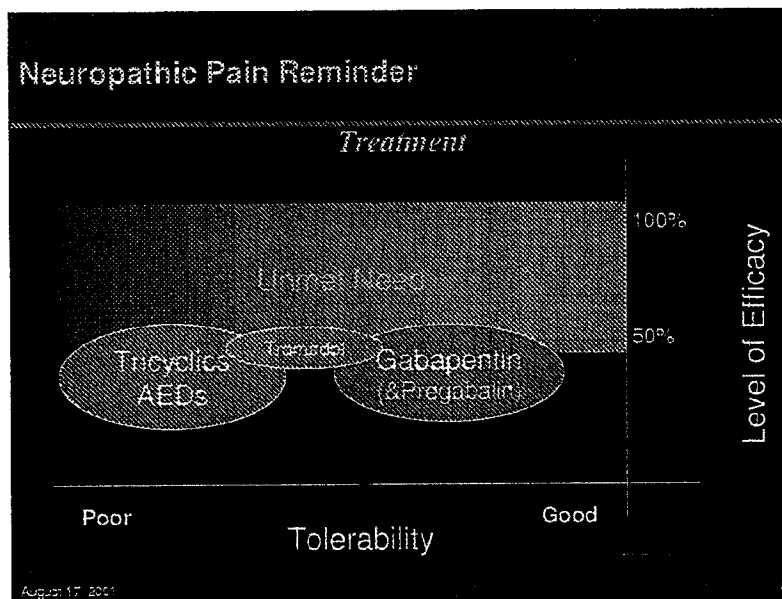
- Greater mean pain reduction and responder rates in site-based pain measurements

- TOLERABILITY & SAFETY

- Dose dependent increase in nausea, vomiting, dizziness
  - Nausea: 34-46% • Dizziness: 17-28%
  - Vomiting: 15-21% • Abnormal Dreams: 18-22%
- Significant Discontinuation Rate: 66% due to AE at 300 mcg BID

August 17, 2007

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## Neuropathic Pain Market

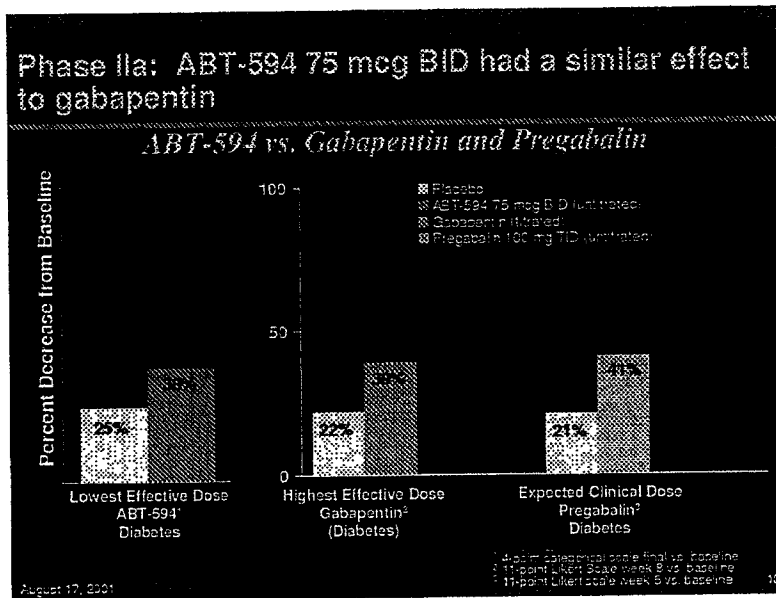
		2000 Rx (MM)	2000 sales (\$MM)	Rx CAGR (96-2000)	Sales CAGR (96- 2000)
Total:	US	10.6	\$470	6%	45%
	Ex-US	18.1	\$235	11%	24%
Gabapentin:	US	3.9	\$352	80%	94%
	Ex-US	1	\$42	125%	191%

Source: Decision Resources; IMS factored analysis

- Growth of sales for neuropathic pain agents exceeds Rx growth
  - Driven by continued growth of the branded and premium priced gabapentin (Neurontin), at the expense of other anti-epileptics and generic tricyclic antidepressants.

August 17, 2001

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**Phase IIa: ABT-594 75 mcg BID untilrated was relatively well tolerated**

Event	Amitriptyline 150 mg d <sup>-1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	56%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

<sup>1</sup> Max: 1507 (n=29)  
<sup>2</sup> M100-625 and M50-633 combined  
 N/A = Not Available

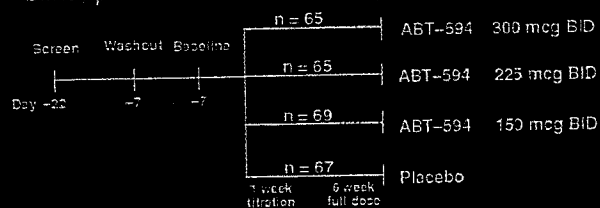
August 17, 2001

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## Phase IIb Study in Neuropathic Pain (M99-114)

### Design

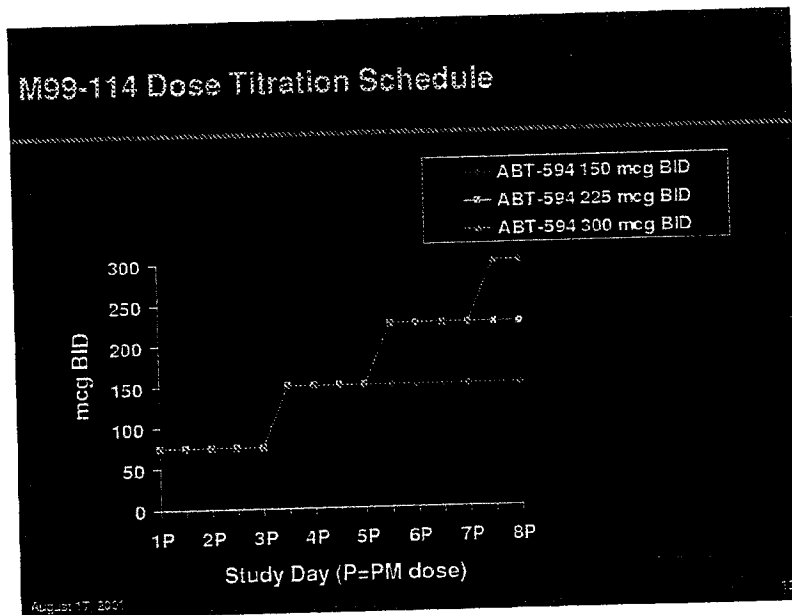
- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-day titration phase: treatment visits at 2, 3, 5 and 7 weeks
- Power
  - Planned: 80% for ES 0.45 with 80 group
  - Study: 60% for ES 0.45 with 66 group (ES 0.65 for pre-based participating people)
- Concomitant analgesics disallowed

August 17, 2001

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Premature Terminations increased with increasing doses of ABT-594

*Subject Disposition*

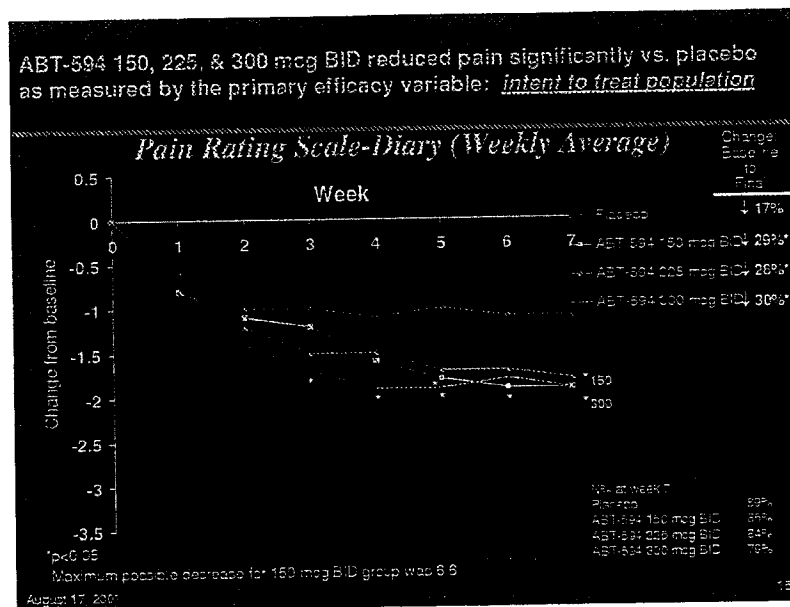
Reason for Discontinuation	Placebo	% of Subjects Discontinuing ABT-594		
		150 mcg BID	225 mcg BID	300 mcg BID
Adverse Event	9	28	46	66
Lack of Efficacy	9	9	3	7
Lost to Follow-up	0	0	1	3
Withdraw Consent	3	5	9	7
Other	2	2	4	3
Total Discontinuation	22	38	57	75

Percentages may not sum correctly due to rounding

August 17, 2007

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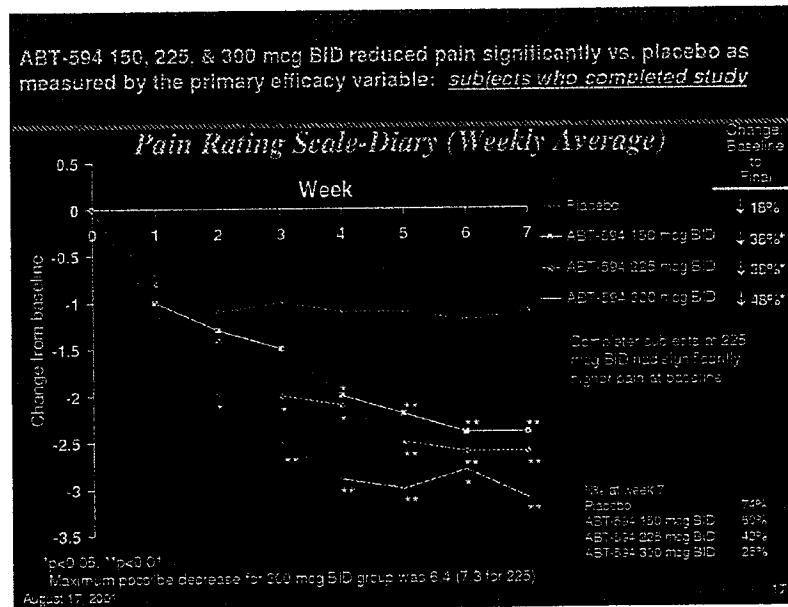


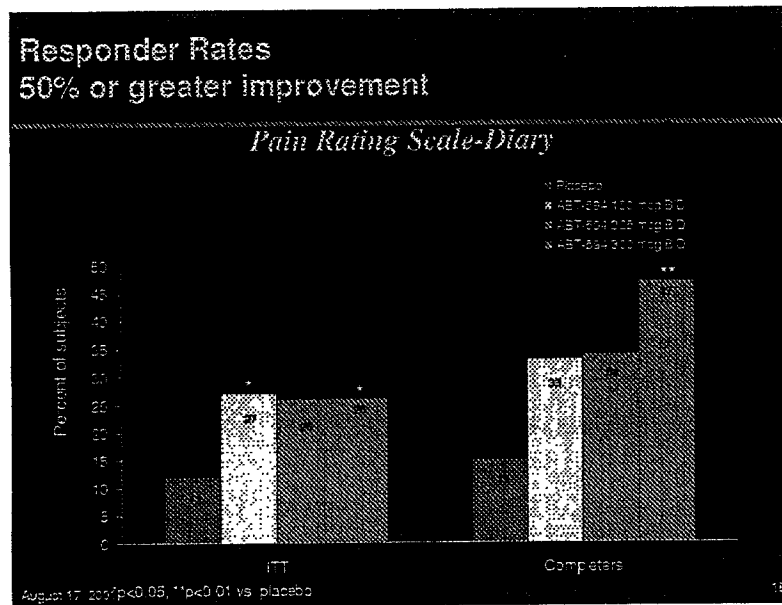


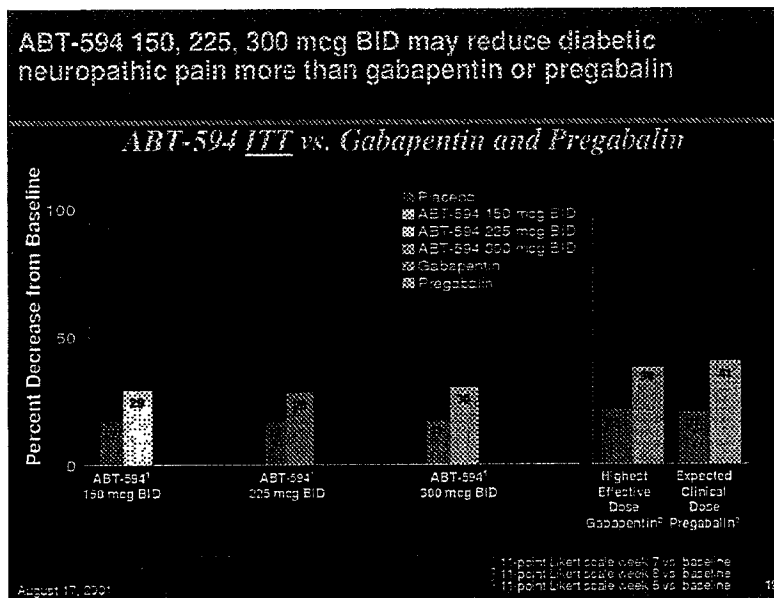
**Completer analysis may predict upside potential of ABT-594**

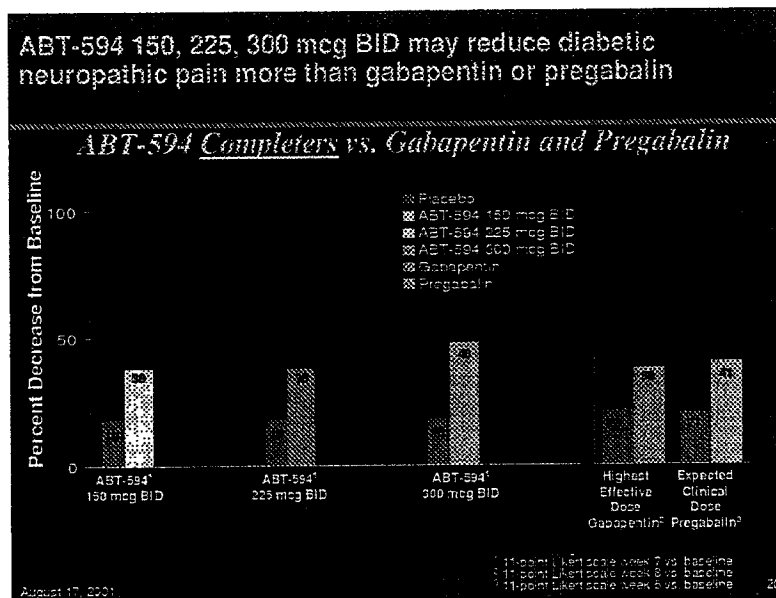
ITT	Completer
<i>Advantages</i>	
More rigorous evaluation of study results	Potential to predict upside of efficacy if all patients were able to complete study
<i>Disadvantages</i>	
Handicapped prediction of upside potential of efficacy given high discontinuation rate (especially early)	Patients who completed the Phase IIB study may not predict accurately efficacy if all patients could tolerate ABT-594

August 17, 2001









### Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg d <sup>-1</sup>	Gabapentin 3600 mg d <sup>-1</sup>	Pregabalin 300 mg d <sup>-1</sup>	ABT-594 150 mcg BID	ABT-594 300 mcg BID
Confusion	N/A	3%	5%	0%	1%
Somnolence	66%	23%	24%	2%	0%
Dizziness	28%	24%	27%	17%	28%
Nausea	N/A	6%	N/A	34%	46%
Vomiting	N/A	N/A	N/A	15%	21%
Peripheral edema	N/A	N/A	7%	0%	0%
Constipation	14%	N/A	N/A	3%	7%
Dry mouth	90%	N/A	N/A	3%	1%

<sup>1</sup> Max. 150% (n=22)  
N/A = Not Available

August 17, 2004

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Efficacy and safety did not vary consistently by subject characteristics

- Smoker/Non-smoker
- Male/Female
- Weight
- Age
- Renal Function

August 17, 2001 22



ABT-594 150, 225 and 300 mcg BID were not associated with clinically meaningful changes in vital signs, ECGs or laboratory data

- Vital signs
- ECG
- Laboratory data

August 17, 2007

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Phase IIb Study in Neuropathic Pain (M99-114)

*Conclusions*

- ABT-594 significantly reduces diabetic neuropathic pain
- ABT-594, as administered without additional improvements in tolerability, has a narrow therapeutic window
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

August 17, 2001

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## ABT-594 Options

- A: Attempt tolerability improvement with ABT-594
  - Explore more prolonged titration
  - Co-administer anti-emetic
  - Protocol Ready
    - 7, 11, 24 day titrations
    - Co-administered anti-emetic during titration
    - Detailed assessments of adverse events
    - \$2.1 MM fully burdened
- B: No additional experiments with ABT-594
- Subtype selective NNR for pain back-up

August 17, 2005

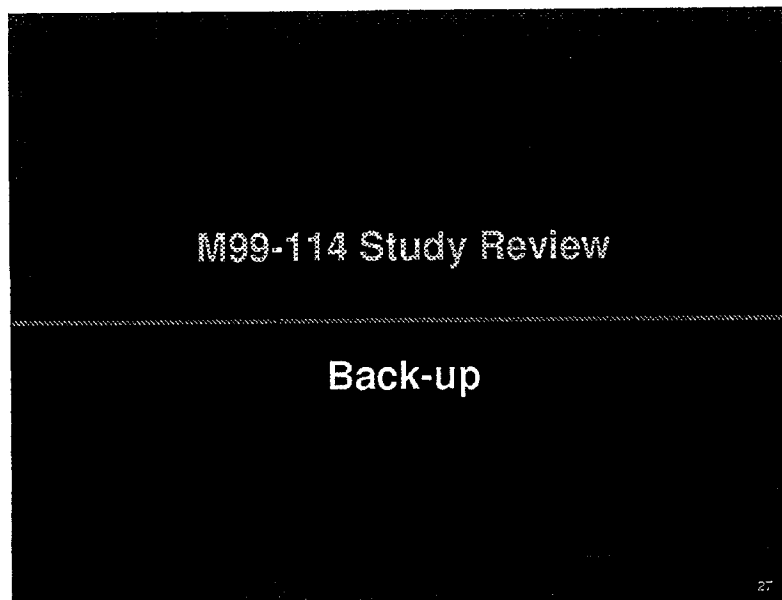
25

## Rationale for Titration and/or co-administration of an anti-emetic to improve tolerability of ABT-594

- Titration
  - General hypotheses
    - Adverse event tolerance
    - Homeostasis
  - Evidence
    - Attenuation of AEs over time in earlier studies, especially doses  $\leq 75$  mcg BID
      - Not observed clearly in Phase Ib at 150, 225 or 300 mcg BID
    - Preclinical evidence of attenuation over time
    - Titration is used to improve the tolerability of most analgesic, neurological and psychiatric drugs
- Anti-emetic
  - Suppression of priming effect during tolerance/homeostasis
  - Preclinical studies
    - Dopamine antagonists
    - 5-HT<sub>3</sub> antagonists

August 17, 2006

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## M99-114: Neuropathic Pain

### *Outcome Measures*

- \* Primary
  - Weekly average of daily Pain Rating Scale (11-point Likert in a diary)
    - Change from baseline to last 7 days on drug
- \* Secondary
  - Site-based Pain Rating Scale (11-point Likert)
  - Neuropathic Pain Scale
  - Patient Global Impression of Change
  - Clinician Global Impression of Change
  - SF-36

August 17, 2001

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**M99-114: Neuropathic Pain**

---

*Outcome Measures*

• **Pain Rating Scale**

0	1	2	3	4	5	6	7	8	9	10
no pain								worst pain possible		

• **Neuropathic Pain Scale (NPS)**

– 10 items (e.g., sharp, hot, intense), for total 0-100 points

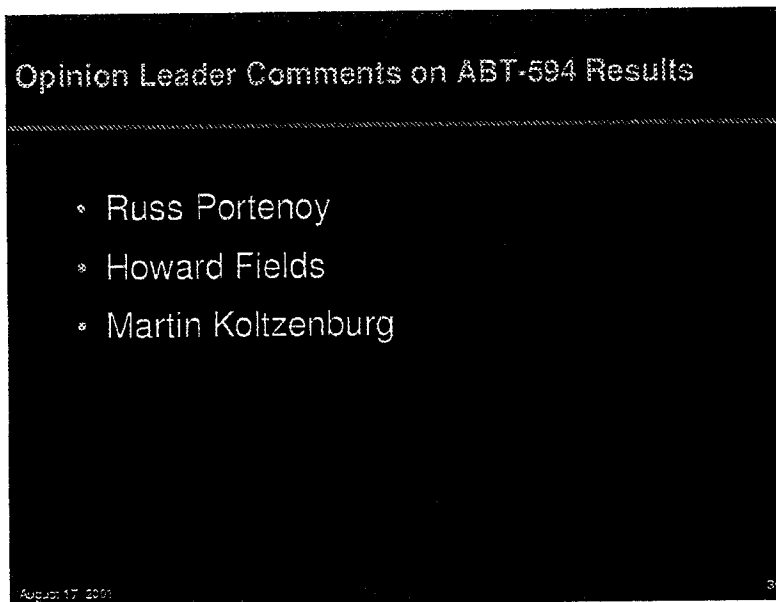
Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10	The most sharp sensation imaginable, like a knife
-----------	---	---	---	---	---	---	---	---	---	----	---

• **Subject, Clinician Impression of Change**

1	Much Improved
2	Moderately Improved
3	Minimally Improved
4	No Change
5	Minimally Worse
6	Moderately Worse
7	Much Worse

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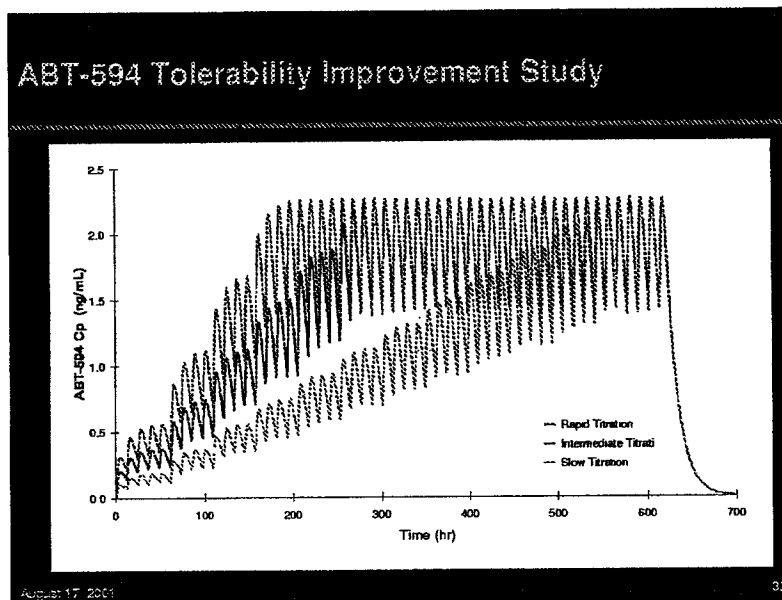


### ABT-594 Tolerability Improvement Study

- \* Controlled, randomized, double-blind, placebo-controlled Phase I
- Adequately powered
- Five Groups:
  - Placebo
  - 7 Day titration ± anti-emetic up through steady state
  - 11 Day titration
  - 24 Day titration

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### Titration Is Used to Improve the Tolerability of Most Analgesic, Neurological and Psychiatric Drugs

#### *Tramadol in naïve patients: Ruoff Study*

	1 Day to 200 mg/day n=130	4 Days to 200 mg/day n=129	10 Days to 200 mg/day n=132
Nausea	28%	31%	21%
Vomiting	10%	12%	8%
Dizziness	24%	19%	8%
Discontinuation Due to AEs	31%	24%	15%

- Patients with chronic joint pain treated with daily NSAIDs and requiring additional pain relief

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Efficacy does not differ by gender

*Pain Rating Scale-Diary (ITT)*

Mean Pain Reduction (%) Baseline to Final

	ABT-594 All Doses n=74/93	ABT-594 150 mcg BID n=26/30	ABT-594 225 mcg BID n=27/31	ABT-594 300 mcg BID n=21/32
Female	27%	33%	26%	25%
Male	28%	31%	24%	30%

VERIFY—NOT CONSISTENT WITH AVG

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### Titration Is Used to Improve the Tolerability of Most Analgesic, Neurological, and Psychiatric Drugs

#### *Tramadol in intolerant patients: Petrone Study*

	10 Days to 200 mg/day n=54	16 Days to 200 mg/day n=59	13 Days to 150 mg/day n=54
Nausea	54%	42%	33%
Vomiting	19%	12%	7%
Dizziness	7%	7%	7%
Discontinuation Due to AEs	54%	34%	30%

- Patients who had discontinued due to nausea or vomiting during a rapid escalation of tramadol dose (4 days to 200 mg/day) were enrolled in the titration evaluation.
- Patients with chronic pain treated with daily NSAIDs.

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### Hypotheses for ABT-594-induced Emesis

- Parenteral administration also elicits emesis in preclinical studies
- No models exist to determine the relative contribution of central and peripheral actions of ABT-594 in emesis

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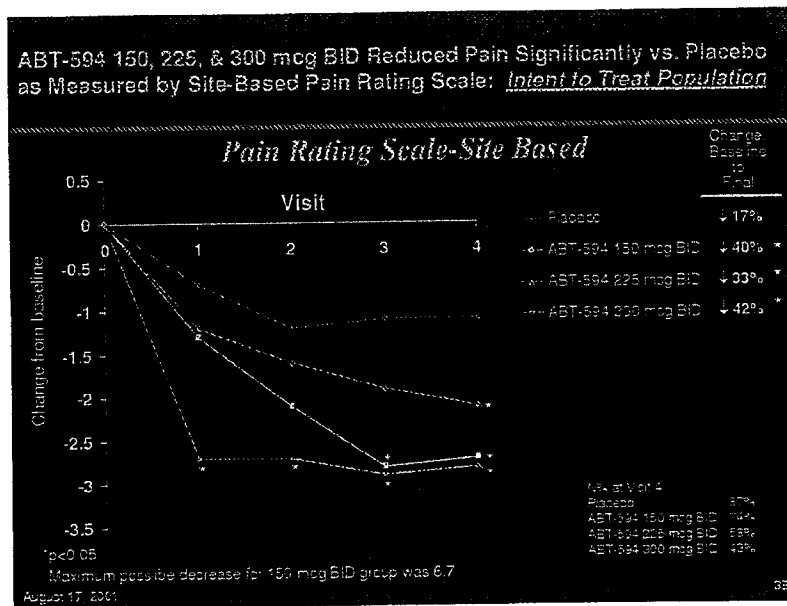
35

### ABT-594 Parenteral

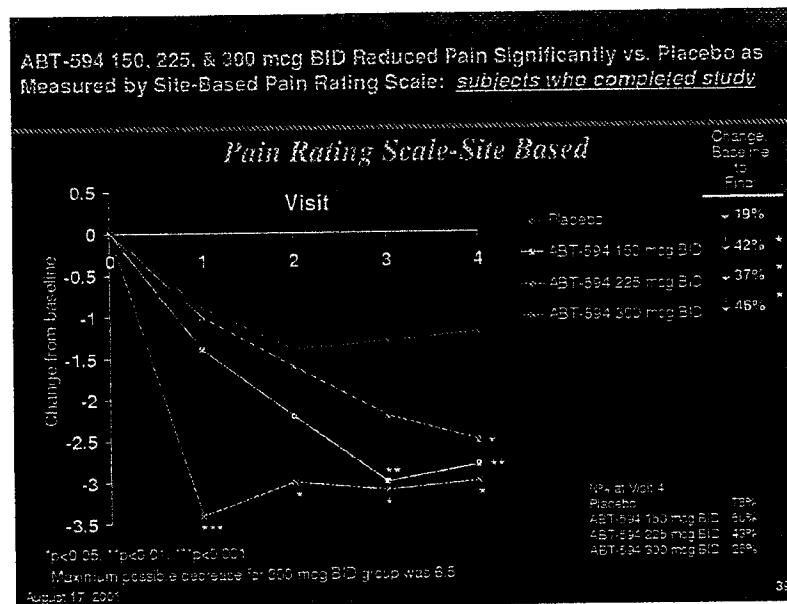
- An option to evaluate different rates-of-rise under single dose administration
- Additional preclinical experiments required
  - More fully explore safety of different rates-of-rise
  - Parenteral drug safety studies
- Formulation development
- Time & Cost
  - EST 6 months
  - EST \$ 0.5 MM

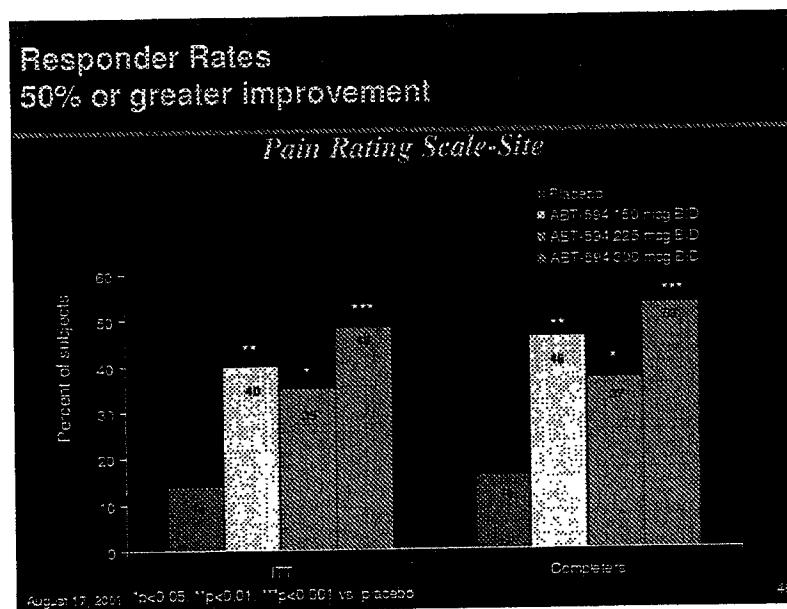
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## M99-114 Neuropathic Pain

### *Summary*

#### • Initial Questions

- Where do doses evaluated to date fit on the dose-response curve?
  - PK/PD effect?
- Can tolerability be improved?
  - Differentiation of patient populations
  - Dosage administration
- If tolerability is improved, will there be even more efficacy?
- How much will patients benefit from ABT-594?
  - If administered as in M99-114
  - Given hypothetical improvements in tolerability & efficacy

#### • Conclusions

- ABT-594 significantly reduces diabetic neuropathic pain
- ABT-594, as administered without any optimization, has a narrow therapeutic window
- ABT-594 has the potential to be an important treatment for neuropathic pain: additional analyses will evaluate the probability that differentiation of patient populations or changes in dosage administration can improve therapeutic index

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**ABT-594 IS A MAJOR SCIENTIFIC ACHIEVEMENT**

- *Independent of future business decisions regarding ABT-594...*
  - ABT-594 is the first drug ever to be successfully discovered and developed with the intent purpose to treat neuropathic pain (and other pain disorders).
  - NNRs are now fully validated as a viable mechanism to treat neuropathic pain
  - For the first time in decades there is now an additional class of analgesic agents:
    - NNRs
    - OPIOIDS
    - NSAIDs/COX-2s
    - ACETAMINOPHEN
    - TCAs/AEDs

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Treatment Groups Were Similar in Terms of Demographics at Baseline

*M99-114 Baseline Characteristics*

		All Patients (N=266)
Gender	Female	45%
	Male	55%
Race	White	69%
	Black	9%
Age	Mean	62
	Range	20-86
Weight	Mean	202
	Range	112-278
Nicotine Use	Former	36%
	Never	53%
	Current	11%

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Treatment Groups Were Similar in Terms Pain at Baseline

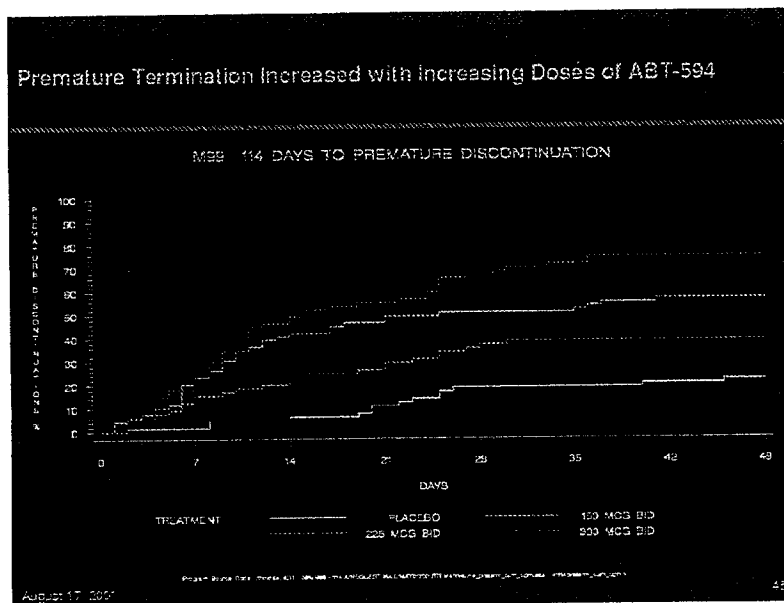
*M99-114 Baseline Characteristics*

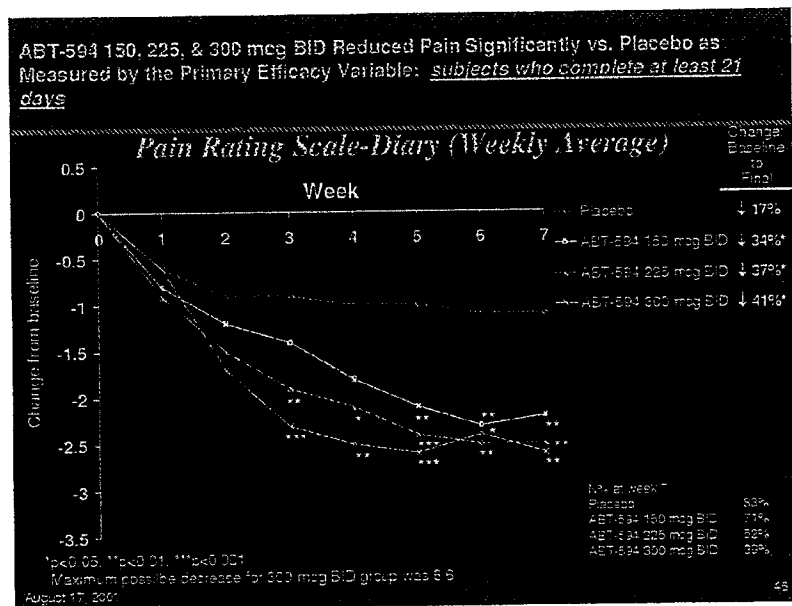
	Placebo	ABT-594 150 mcg BID	ABT-594 225 mcg BID	ABT-594 300 mcg BID	ABT-594 All Female	ABT-594 All Male
Pain Rating Scale Diary (10)	6.5	6.5	6.7	6.7	**7.0	**6.4
Pain Rating Scale Site (10)	6.5	6.7	6.7	6.9	**7.1	**6.4
Neuropathic Pain Scale (100)	56.5	55.1	55.3	57.3	***60.6	***52.2

\*\* p<0.01, \*\*\* p<0.001 (female vs. male)

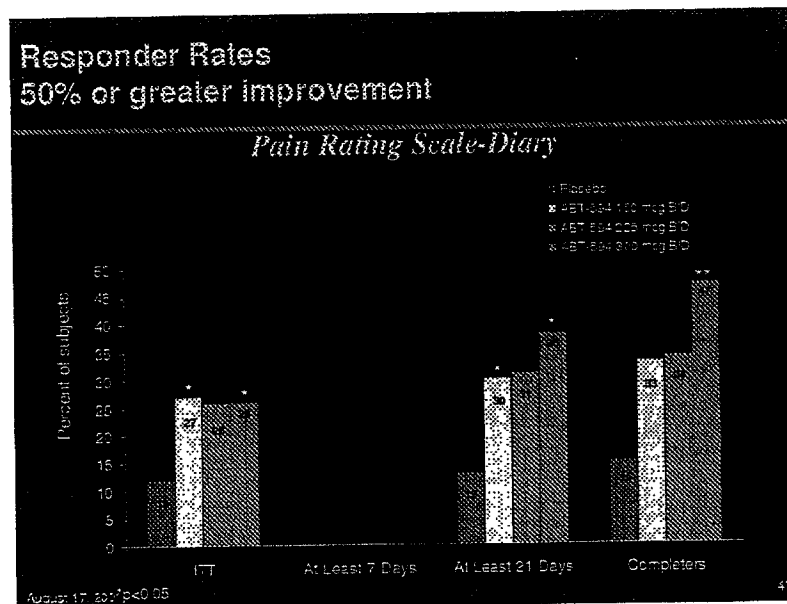
August 17, 2001

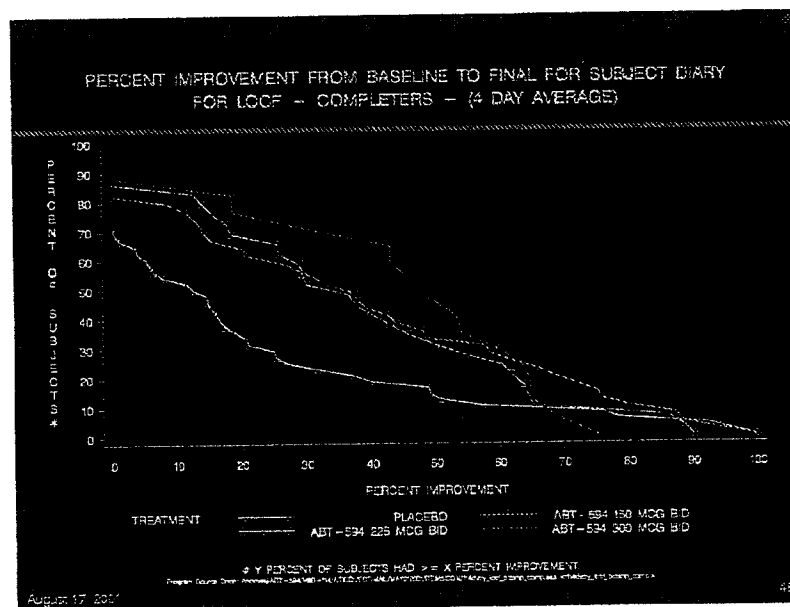
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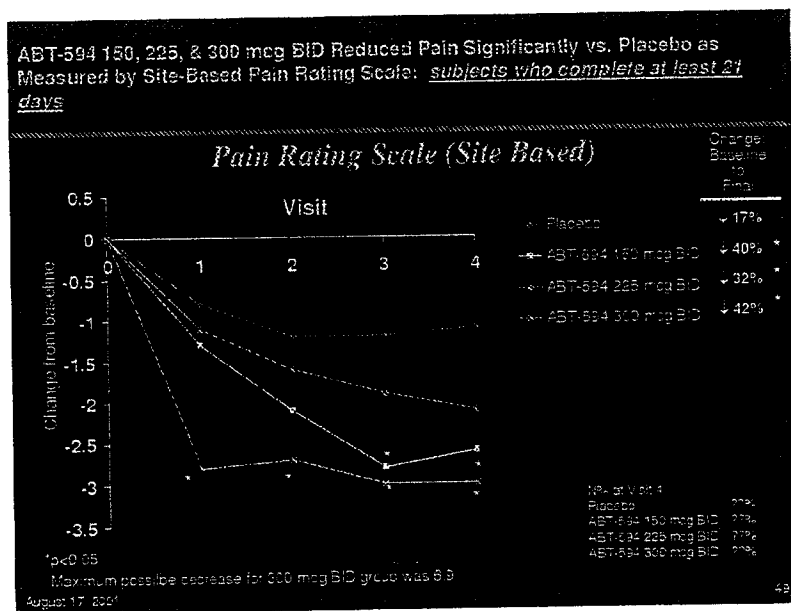


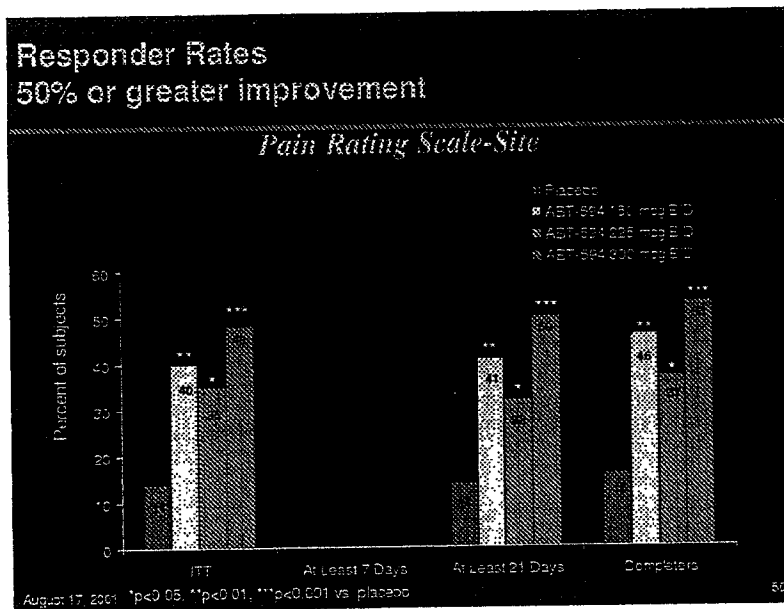


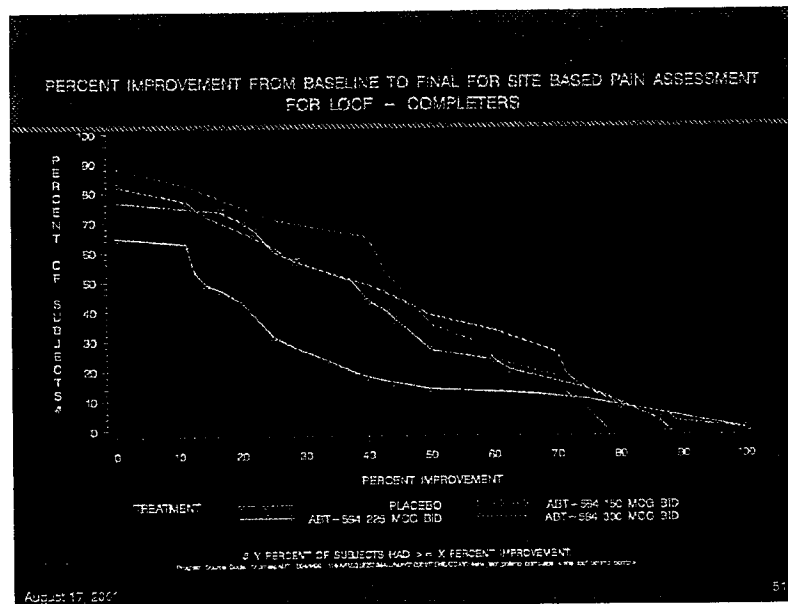


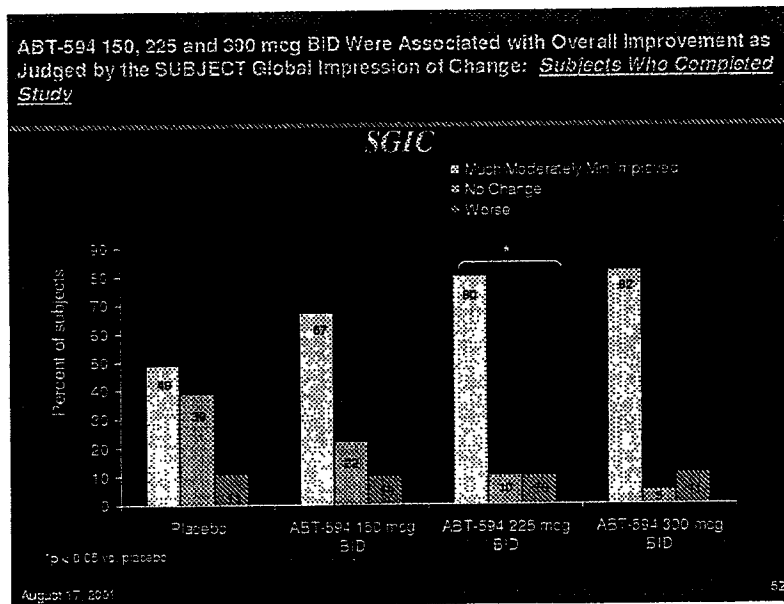


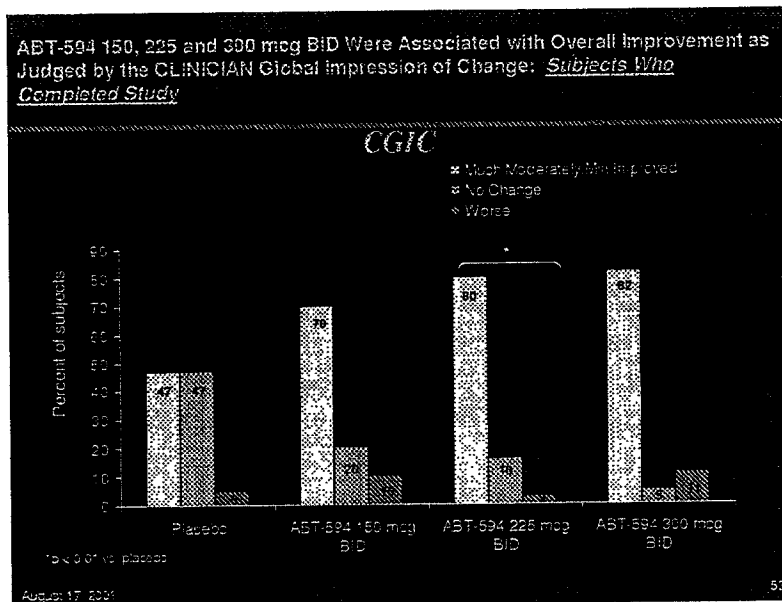


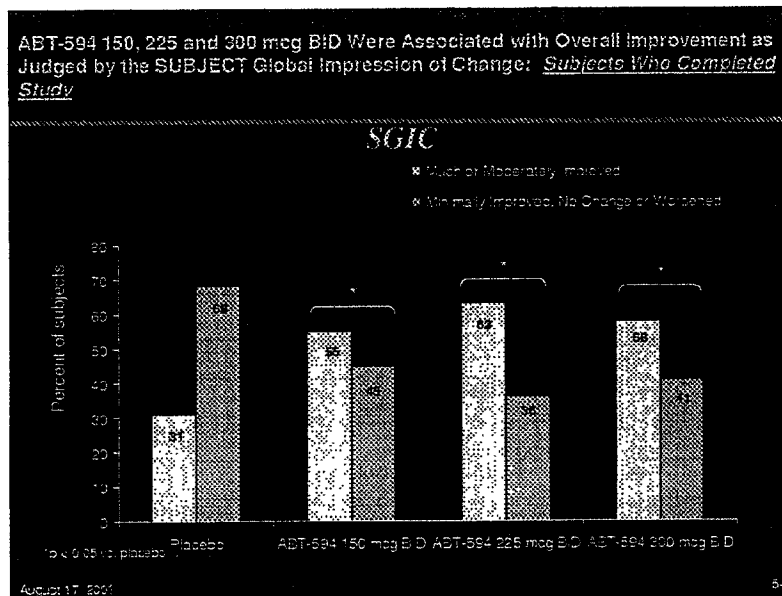




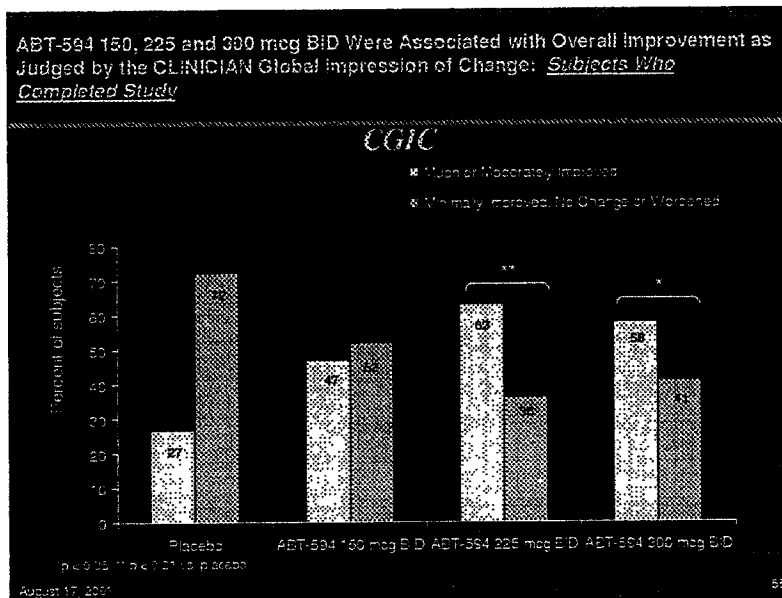


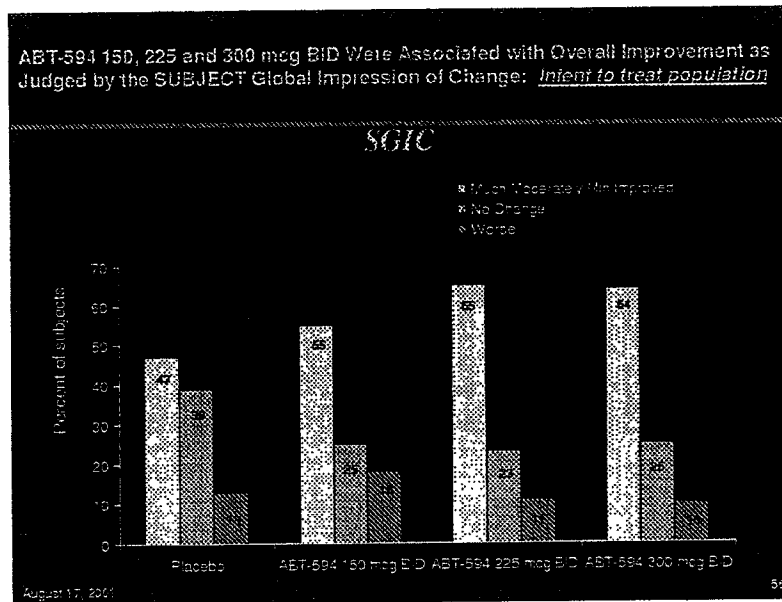


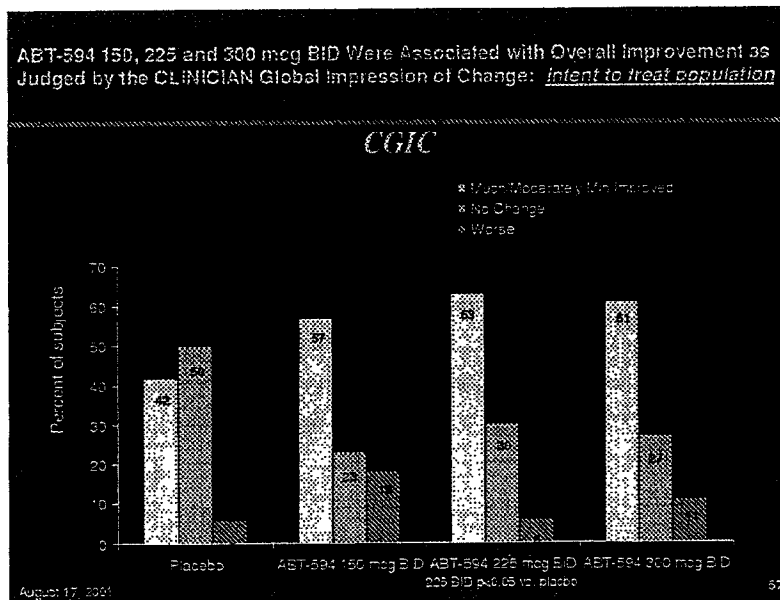


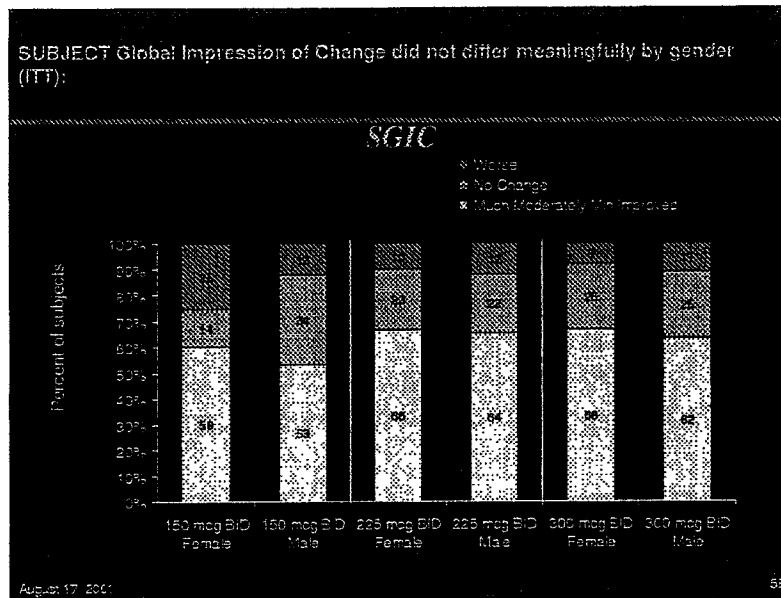


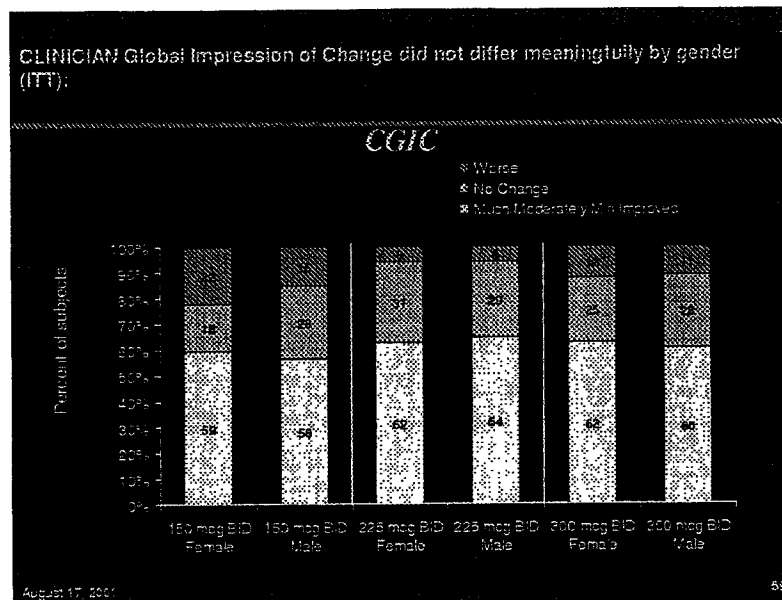


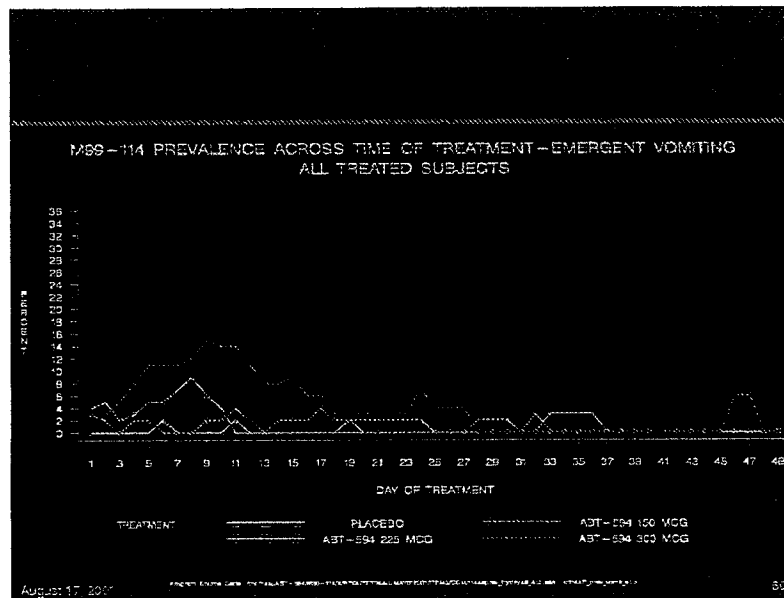


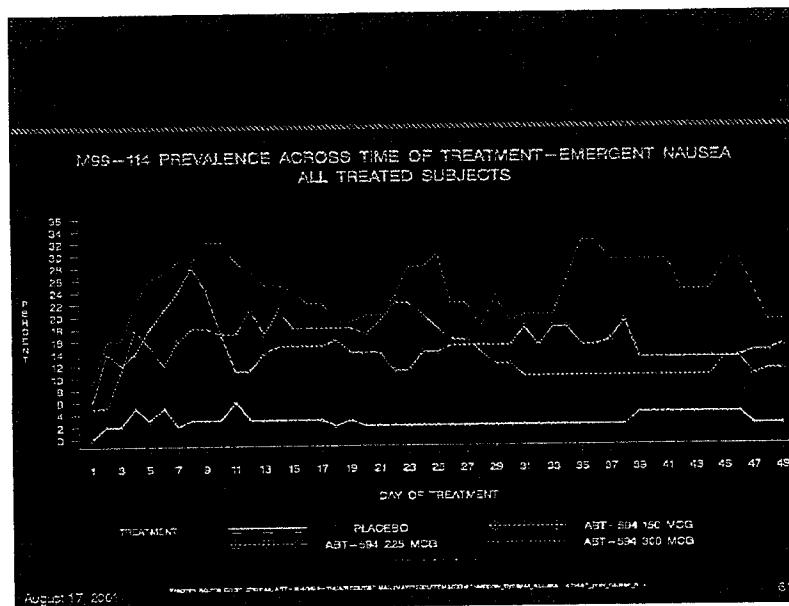


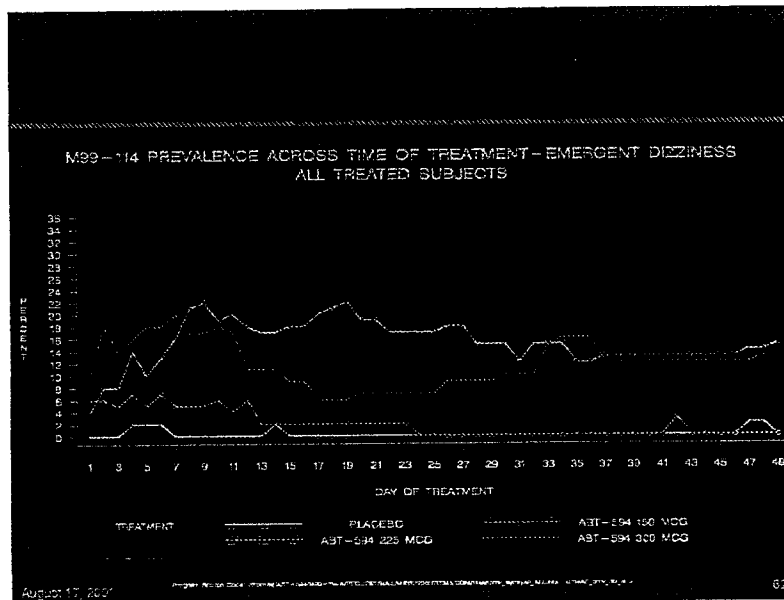




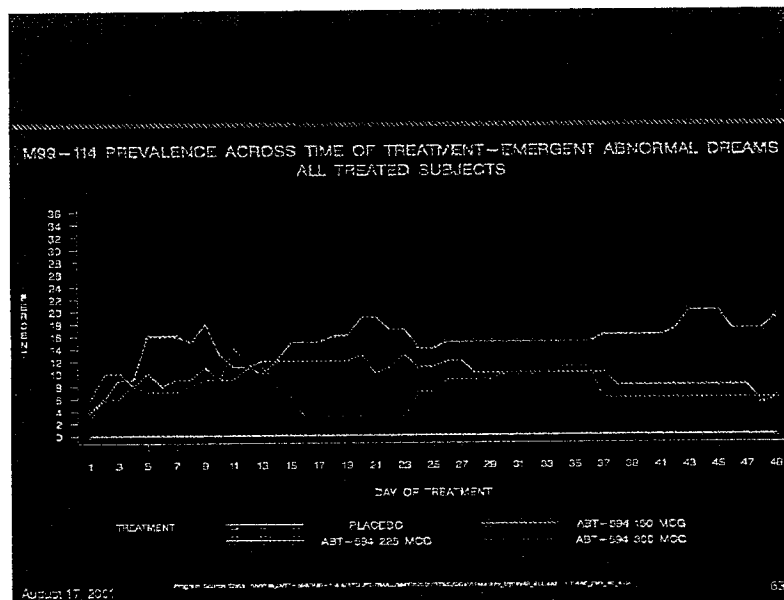












## Adverse Event Differences by Gender

*150 mcg BID*ABT-594  
150 mcg BID

	Female (N=31)	Male (N=34)
Diarrhea*	6 (19%)	1 (3%)
Nausea*	15 (48%)	7 (21%)
Vomiting*	7 (23%)	3 (9%)
Abnormal Dreams	9 (29%)	5 (15%)

\*p &lt; 0.05

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Adverse Event Differences by Gender		
<i>225 mcg BID</i>		
	ABT-594 225 mcg BID	
	Female (N=33)	Male (N=36)
Asthenia	7 (21%)	4 (11%)
Dyspepsia	2 (6%)	6 (17%)
Nausea	18 (55%)	12 (33%)
Vomiting	11 (33%)	6 (17%)
Abnormal Dreams	9 (27%)	6 (17%)
Dizziness	10 (30%)	14 (39%)

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Adverse Event Differences by Gender		
<i>300 mcg BID</i>		
ABT-594		
300 mcg BID		
	Female (N=30)	Male (N=37)
Asthenia	9 (30%)	4 (11%)
Diarrhea	3 (10%)	1 (3%)
Nausea	15 (50%)	16 (43%)
Vomiting	4 (13%)	10 (27%)

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### Completers vs. Preterms: initial analysis

- Significant Differences
  - Gender
    - Males were more likely to complete at 150 mg (80% vs. 20% for males; 42% vs. 58% for females)
    - More females than males preterm due to adverse events (55% vs. 39%) when all ABT-594 groups were combined
  - Baseline Pain
    - Preterms had lower baseline pain than completers at 225 mg B.D. (6.3 vs. 7.3, PRS diary)
  - Weight & Height
    - Preterms had lower weight & height than completers when ABT-594 groups were combined (196 vs. 207 lbs)
  - Nicotine Use
    - Fewer users and ex-users prematurely terminated than never users when all ABT-594 groups were combined (39% vs. 53%)
- No differences
  - Gender (225, 300)
  - Race
  - Age

August 17, 2001 — Baseline Pain (N=50, 300)

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# Completers vs. Preterms: Adverse Events

150 mcg BID

ABT-594  
150 mcg BID

	Completer (N=40)	Preterm (N=25)
Diarrhea	3 (8%)	4 (16%)
Nausea	10 (25%)	12 (48%)
Vomiting*	3 (8%)	7 (28%)
Abnormal Dreams	6 (15%)	8 (32%)
Dizziness*	3 (8%)	8 (32%)

Adverse events > 10% more common in preterm  
\*p < 0.05

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### Completers vs. Preterms: Adverse Events

225 mcg BID

ABT-594

225 mcg BID

	Completer (N=30)	Preterm (N=39)
Headache	3 (10%)	7 (18%)
Nausea	9 (30%)	21 (54%)
Vomiting*	3 (10%)	14 (36%)
Dizziness	9 (30%)	15 (38%)
Insomnia	2 (7%)	7 (18%)
Nervousness	0	4 (10%)

Adverse events > 10% more common in preterm  
\*p < 0.05

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### Completers vs. Preterms: Adverse Events

300 mcg BID

ABT-594  
300 mcg BID

	Completer (N=17)	Preterm (N=50)
Asthenia	2 (12%)	11 (22%)
Vomiting	1 (6%)	13 (26%)
Abnormal Dreams	1 (6%)	11 (22%)
Insomnia	1 (6%)	6 (12%)
Nausea	8 (47%)	23 (46%)
Dizziness	6 (35%)	13 (26%)

Adverse events > 10% more common in preterm

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Completers vs. Preterms: Adverse Events		
<i>All ABT-594 Subjects</i>		
	ABT-594 All Subjects	
	Completer (N=87)	Preterm (N=114)
Nausea*	27 (31%)	56 (49%)
Vomiting*	7 (8%)	34 (30%)
Abnormal Dreams	14 (16%)	27 (24%)
Dizziness	18 (21%)	36 (32%)
Insomnia	3 (3%)	14 (12%)

Adverse events > 10% more common in preterm  
\*p < 0.05

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### Premature Termination Benchmarks

- Gabapentin in Diabetic Neuropathy
  - GBP: 17% Total, 8% AE
  - PCB: 20% Total, 6 % AE
- Pregabalin in Diabetic Neuropathy
  - PGB:
- Tramadol in Diabetic Neuropathy

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## Neuropathic Pain Reminder

### Treatment Adverse Events Rates

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d
Confusion	N/A	N/A	3%	5%
Somnolence	66%	53%	23%	24%
Dizziness	20%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

<sup>1</sup> Max. 150T (max 250)  
N/A = Not Available

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ABT-594 150, 225 and 300 mcg BID Were Associated with a Dose Dependent Increase in Adverse Events, Especially Nausea, Vomiting and Dizziness: All Subjects

### *Adverse Events*

	Placebo	ABT-594 150 mcg BID	ABT-594 225 mcg BID	ABT-594 300 mcg BID
Event	N = 65	N = 65	N = 69	N = 67
Nausea	11 %	34 %*	43 %*	46 %*
Abnormal Dreams	0 %	22 %*	22 %*	18 %*
Headache	12 %	20 %	14 %	19 %
Dizziness	5 %	17 %*	35 %*	28 %*
Vomiting	3 %	15 %*	25 %*	21 %*
Diarrhea	3 %	11 %	12 %	6 %
Dyspepsia	3 %	8 %	12 %	7 %
Asthenia	2 %	6 %	16 %*	19 %*

Counting in 15% 150 mcg B.D. ABT-594 treated patients and ABT-594 incidence in placebo  
\*p < 0.05 vs placebo

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95% Confidence Intervals for Nausea, Vomiting and Dizziness

---

*Adverse Events*

	150 mcg BID	225 mcg BID	300 mcg BID
Nausea	34% [22, 45]	43% [32, 55]	46% [34, 58]
Vomiting	15% [7, 24]	25% [14, 35]	21% [11, 31]
Dizziness	17% [8, 26]	35% [24, 46]	30% [19, 41]

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**Increasing Levels of Pain Reduction May Trend with  
Increasing Incidence of Adverse Events at 300 mcg BID**

300 mcg BID (ITT)  
Pain Reduction Quartiles

	Least Pain Reduction n=12	Quartile n=10	Quartile n=16	Most Pain Reduction n=15
Nausea	42%	40%	50%	60%
Vomiting	17%	20%	25%	27%
Dizziness	42%	0%	38%	20%

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**Sample Size Is Too Small to Make Conclusions About  
The Relationship Between Level of Pain Reduction and  
Treatment Emergent Adverse Events for Completers**

300 mcg BID (Completers)  
Quartile Pain Reduction

	Least Pain Reduction n=2	Quartile n=1	Quartile n=6	Most Pain Reduction n=8
Nausea	0%	0%	50%	63%
Vomiting	0%	100%	0%	0%
Dizziness	0%	0%	50%	38%

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QT Assessment

- M99-114 not designed to assess QT
- Mean QT
- Individual QTc (Bazett) Changes (on drug)
  - #4081: From 441 ms to 520 ms
    - Abt (BGM) re-read *would* be from 521 to 439 ms
- Syncope
  - #4083: h/o afib, to ER for "syncope", refuses to release medical records

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## ABT-594

### *Questions*

- Where do doses evaluated to date fit on the dose-response curve?
  - PK/PD Effect
- Can tolerability be improved?
  - Differentiation of patient populations
  - Dosage administration
- If tolerability is improved, will there be even more efficacy?
- How much will patients benefit from ABT-594?
  - If administered as in M99-114
  - Given hypothetical improvements in tolerability & efficacy

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**ABT-594 IS A MAJOR SCIENTIFIC ACHIEVEMENT**

---

- *Independent of future business decisions regarding ABT-594...*
  - ABT-594 is the first drug ever to be successfully discovered and developed with the intent purpose to treat neuropathic pain (and other pain disorders).
  - NNRs are now fully validated as a viable mechanism to treat neuropathic pain
  - For the first time in decades there is now an additional class of analgesic agents:
    - NNRs
    - OPIOIDS
    - NSAIDs-COX-2s
    - ACETAMINOPHEN
    - TCAs/AEDs

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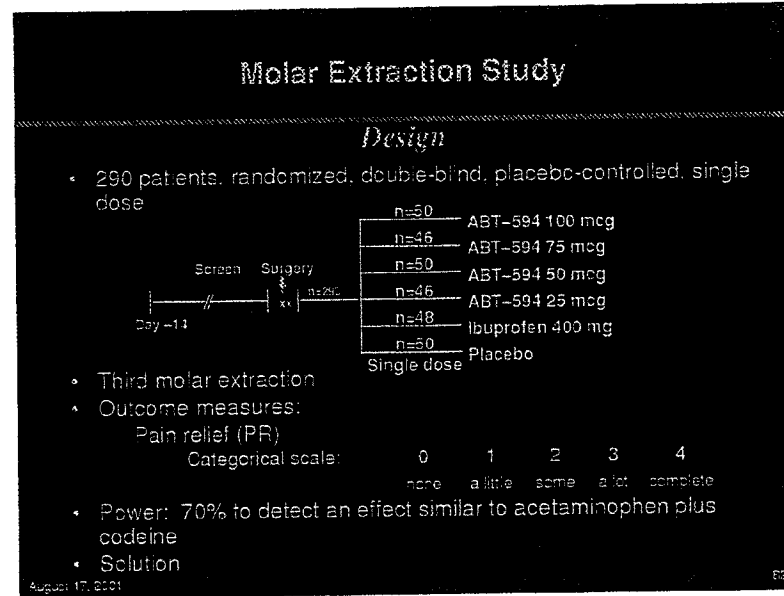
## ABT-594

### *Pharmacokinetics and Metabolism*

- Half-life ( $t_{1/2}$ ): about 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{max}$  similar with/without food
- $T_{max}$  varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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## Molar Extraction Study

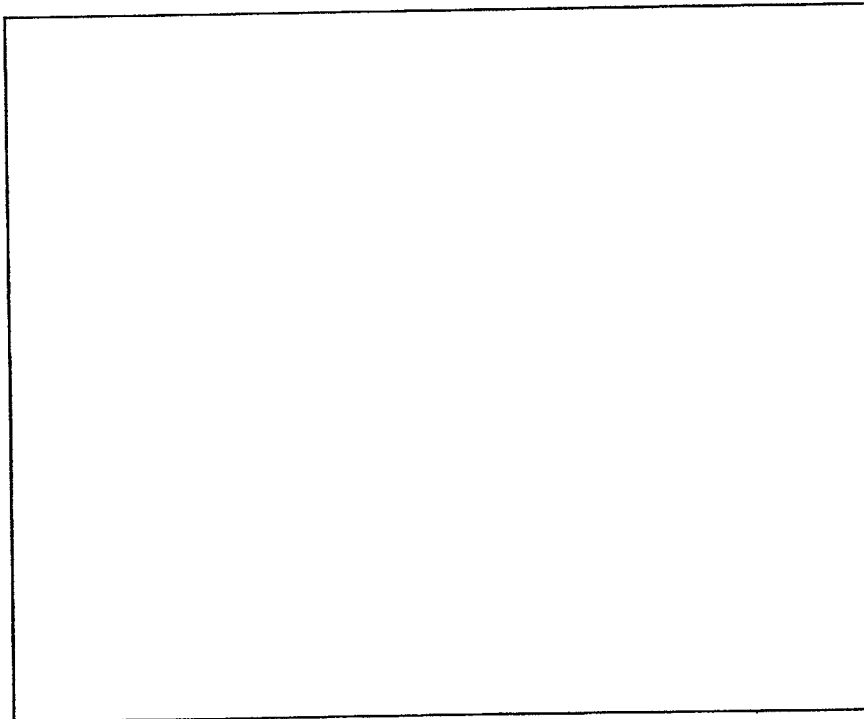
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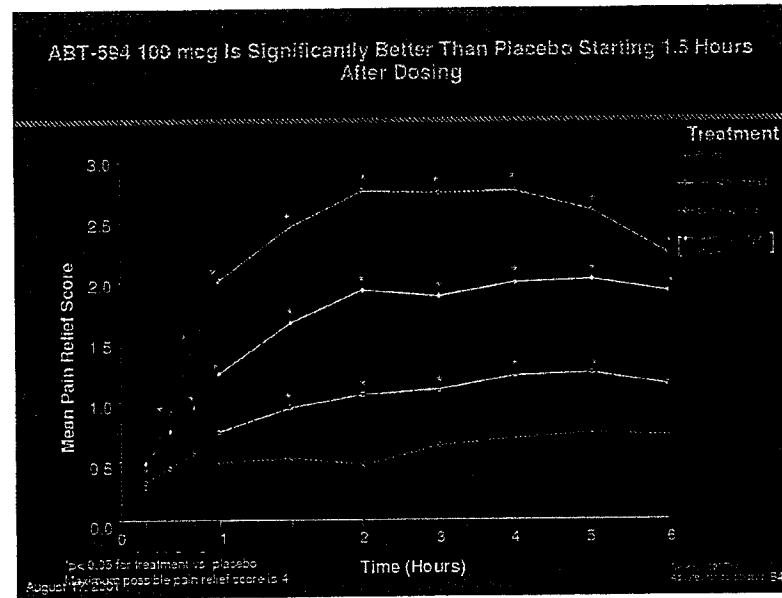
### *Outcome Measures*

- **Pain Relief (PR)**
  - Categorical scale: 0 none 1 mild 2 some 3 a lot 4 complete
- **Total Pain Associated Relief (TOTPAR)**
  - Area under the curve for PR (0-6 hours)
- **Pain Intensity (PI)**
  - Categorical scale: 0 none 1 mild 2 moderate 3 severe
  - Visual Analog Scale:


- **Stop Watch Model**
  - Time to "perceptible" and "meaningful" relief
- **Time To Rescue Medication**
- **Patient Global**
  - Rate medication: 1 poor 2 fair 3 good 4 excellent

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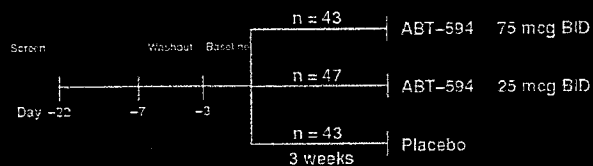




## Neuropathic Pain Pilot

### Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
  - 52% idiopathic      46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

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## Neuropathic Pain Pilot

---

### *Outcome Measures*

- **Pain Intensity (PI)**
  - Categorical Scale:
 

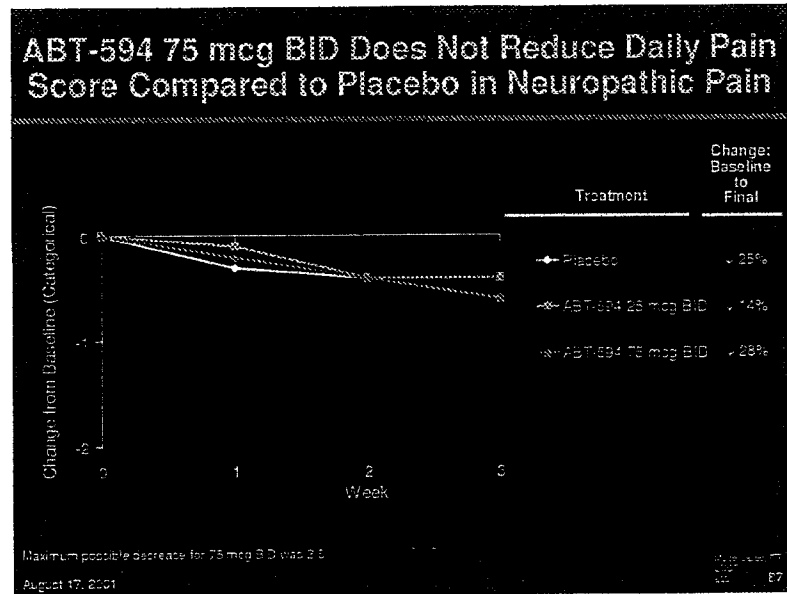
0	1	2	3
none	mild	moderate	severe
  - Visual Analog Scale:  
(0-100 mm)
 

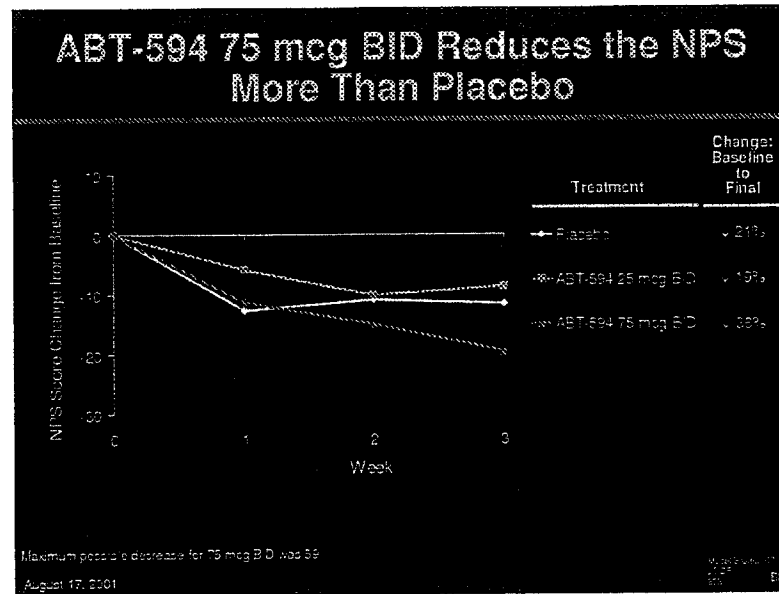
no pain	-----	worst possible
---------	-------	----------------
- **Neuropathic Pain Scale (NPS)**
  - 10 items (e.g., sharp, hot, intense) for total 0-100 points
  - Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"
  - |           |   |   |   |   |   |   |   |   |    |   |    |   |
|-----------|---|---|---|---|---|---|---|---|----|---|----|---|
| not sharp | <table border="1" style="display: inline-table;"> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table> | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8  | 9 | 10 | The most sharp<br>sensation<br>imaginable (like a<br>knife) |
| 1         | 2   | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |   |    |   |
- **Patient Global (PG)**
  - Rate Medication:
 

1	2	3	4
poor	fair	good	excellent

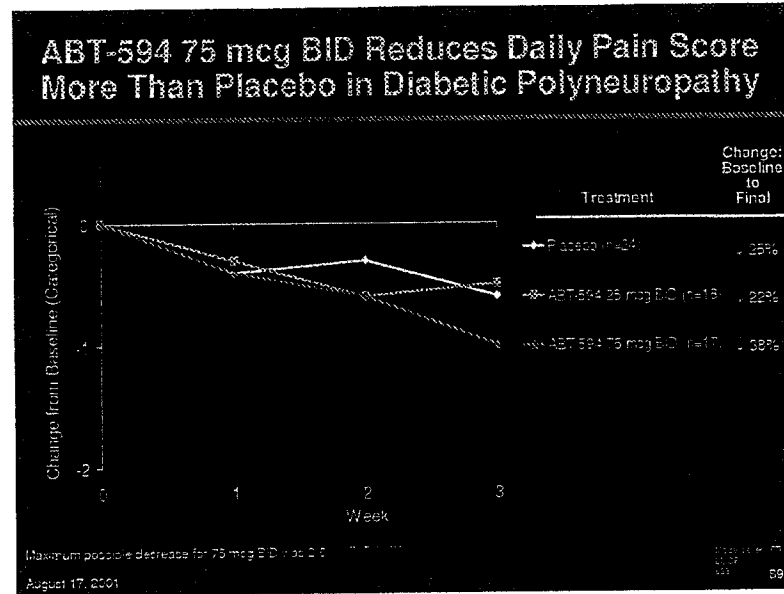
August 17, 2004 ES

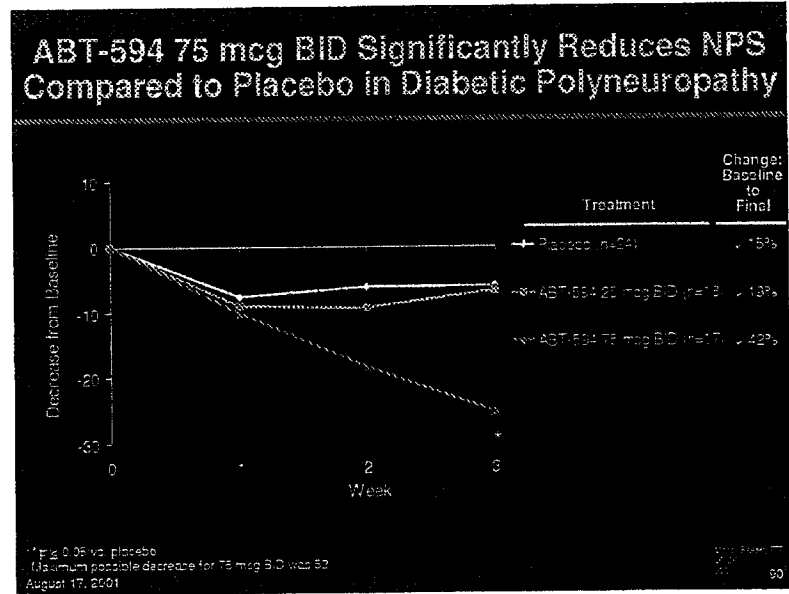


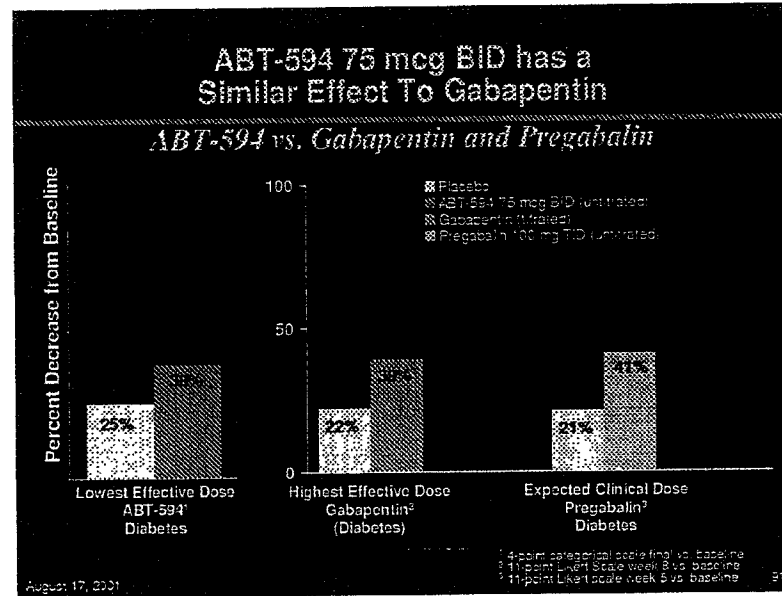




# PART 2



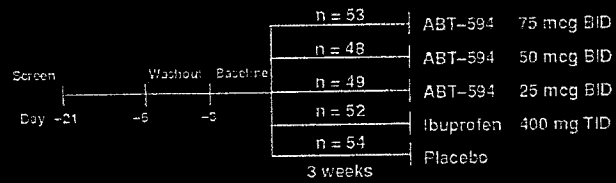




## Osteoarthritis Pain Pilot

### Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

August 17, 2001

92

## Osteoarthritis Pain Pilot Study

---

### Outcome Measures

- Pain Intensity (PI)
  - Categorical Scale:
 

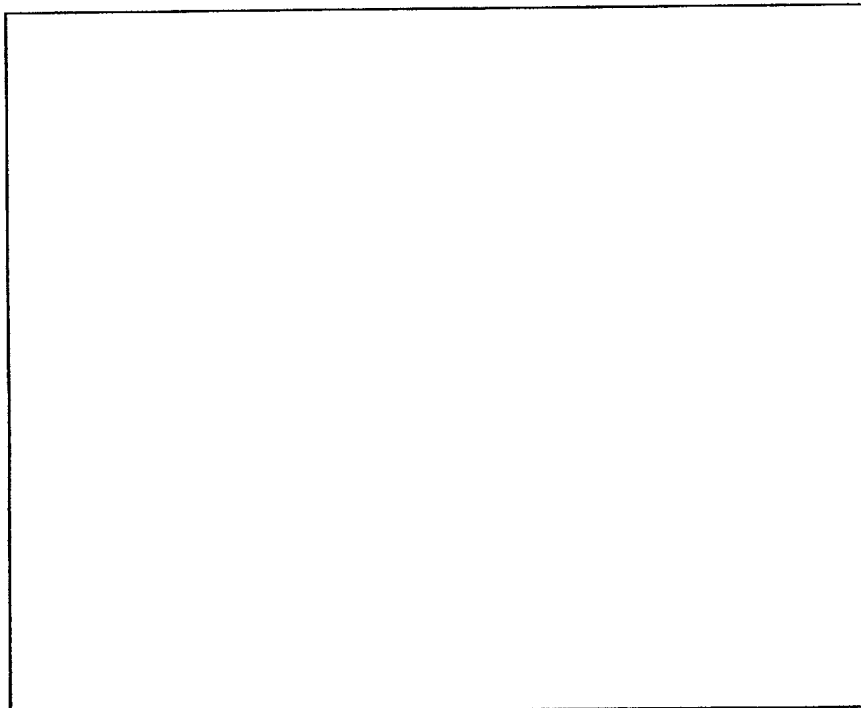
0	1	2	3
none	mil	moderate	severe
  - Visual Analog Scale (VAS)
 

no pain
worst possible
- WOMAC
  - Pain (0-500)
  - Stiffness (0-200)
  - Function (0-1700)

}
Total (0-2400)
- Patient Global
  - Rate Medication:
 

1	2	3	4
poor	fair	good	excellent

August 17, 2001 93





**Osteoarthritis Pain Pilot Study**

---

**WOMAC**

**Pain**      How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain |-----| extreme pain

**Stiffness**      How severe is your stiffness...

- After sitting, lying, or resting later in the day?

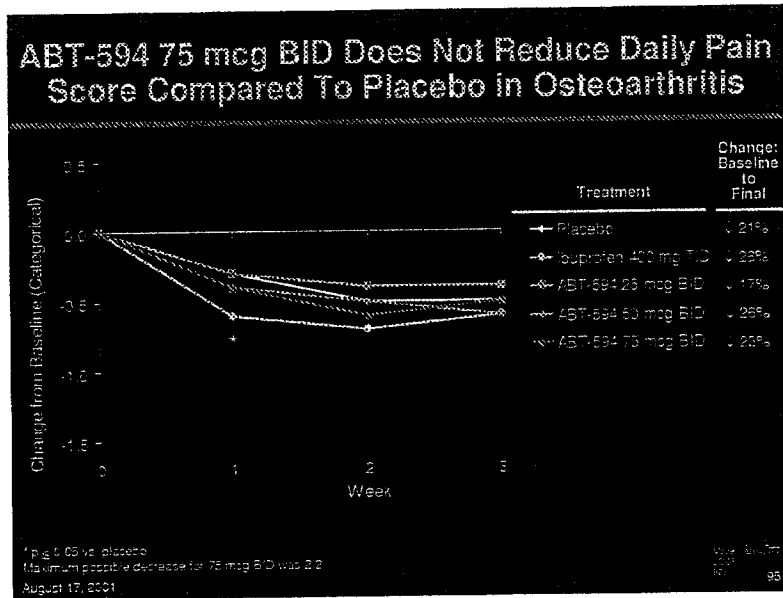
no stiffness |-----| extreme stiffness

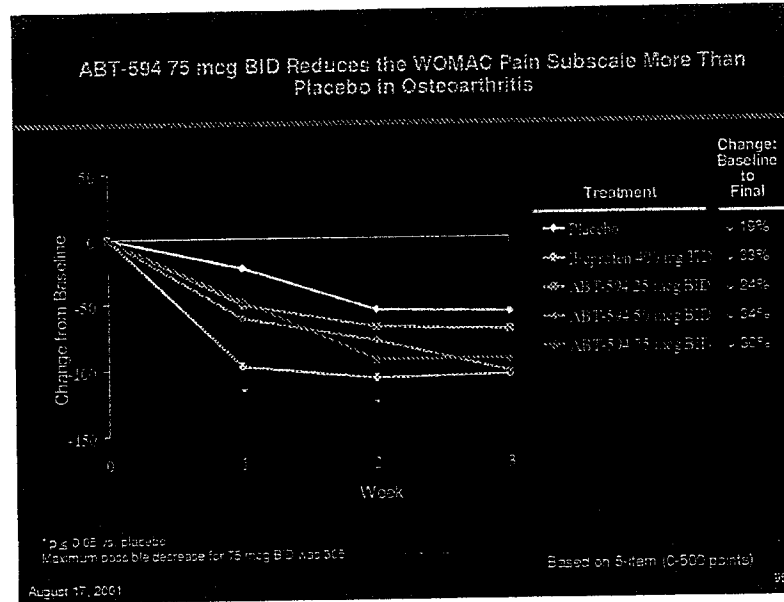
**Function**      What degree of difficulty do you have...

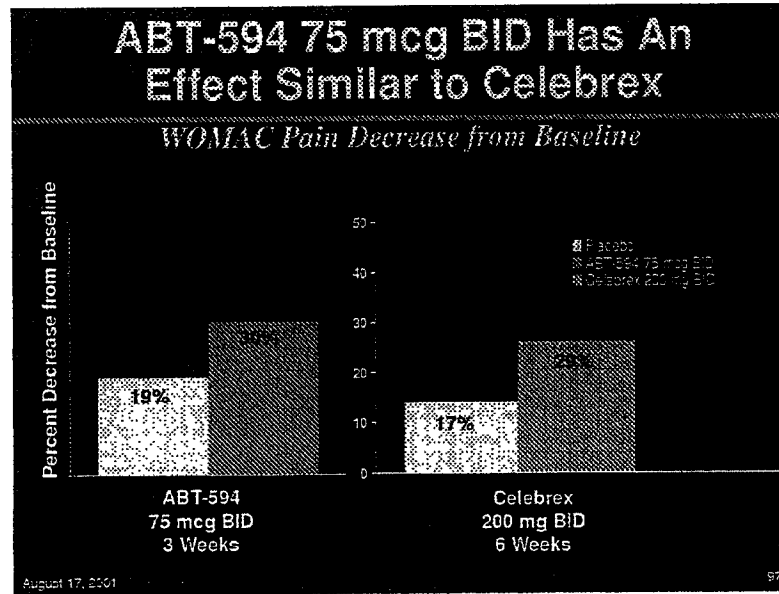
- Descending stairs?
- Rising from bed?

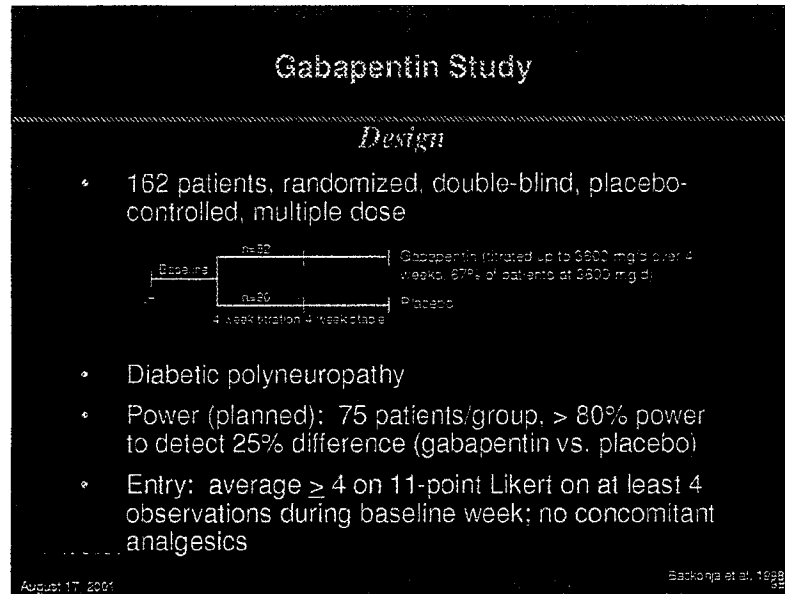
no difficulty |-----| extreme difficulty

August 17, 2001 94









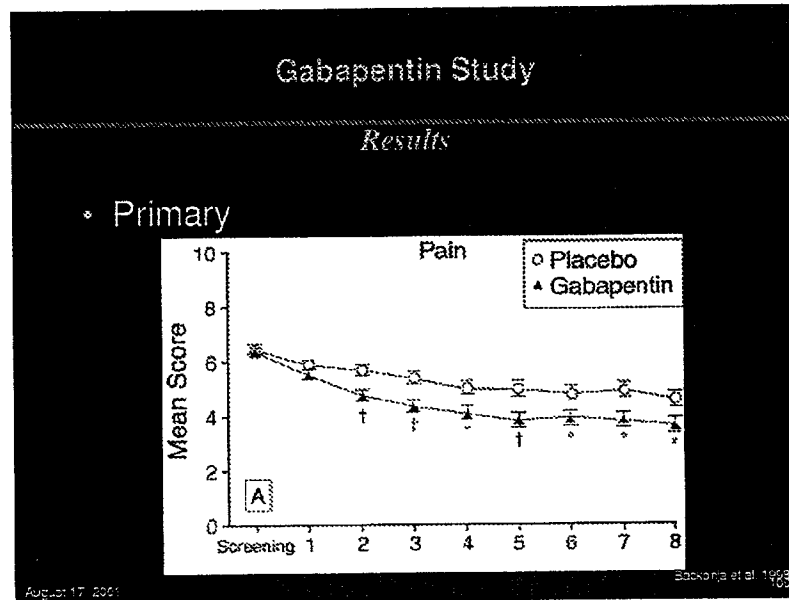
**Gabapentin Study**

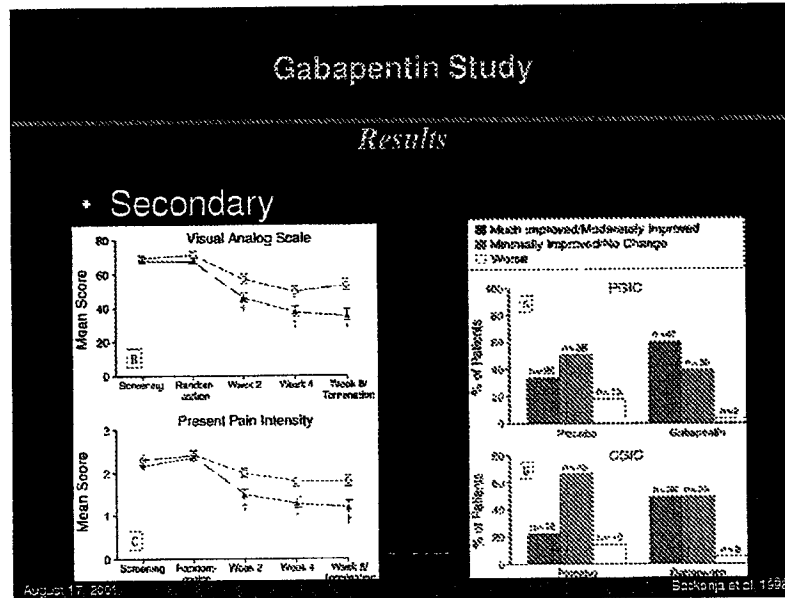
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*Outcome Measures*

- Primary
  - 11-point Likert (0=no pain; 10=worst pain)
- Secondary
  - SFMPQ VAS no pain ————— worst possible pain
  - SFMPQ PPI
    - 0 no pain
    - 1 Mild
    - 2 Discomforting
    - 3 Distressing
    - 4 Horrible
    - 5 Excruciating
  - Patient global impression of change (7 point scale)

August 17, 2001 Baskin et al. 1998







Gabapentin Studies		
<i>Adverse Events</i>		
	<u>Adverse Event Rate (%)</u>	
	Gabapentin	(placebo)
Dizziness	20	(4)
Somnolence	19	(5)
Headache	9	(3)
Diarrhea	9	(7)
Confusion	7	(1)
Nausea	7	(4)

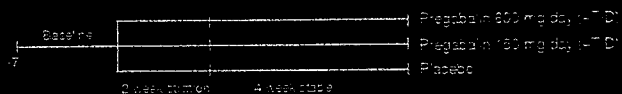
August 17, 2001

Backonja et al. 1998

## Pregabalin Studies

### Design - 014

- 246 patients, randomized, double-blind, placebo-controlled



- Power not specified
- Entry
  - Average  $\geq 4$  on 11-point daily Likert during baseline
- Discontinuation due to adverse events:
 

600 mg/d	8.5%
150 mg/d	2.5%
Placebo	4.7%

August 17, 2001

Sharma et al. 2003

**Pregabalin Studies**

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*Outcome Measures - 014*

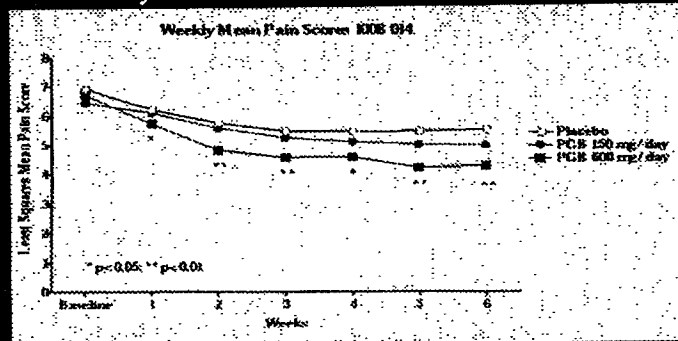
- Primary
  - Weekly mean Likert pain score (probably)
- Secondary
  - Responder rate
  - Patient global impression of change
  - Sleep interference score
  - SFMPQ

August 17, 2001 Sharma et al. 2000

## Pregabalin Studies

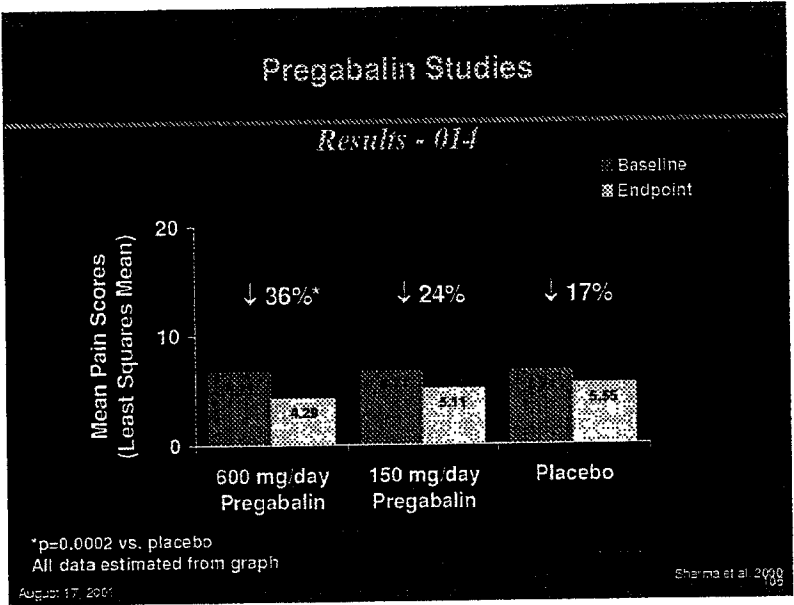
### Results - 014

#### • Primary



August 17, 2001

Sharma et al. 2000



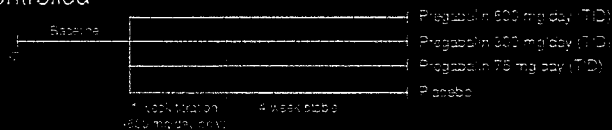
Pregabalin Studies	
<i>Responder Rate - 014</i>	
	Responder Rate
600 mg/day	39%*
150 mg/day	15%
Placebo	12%
Responder = at least 50% reduction in mean baseline pain score	
*p=0.0002 vs. placebo	
August 17, 2007	Sharma et al. 2007

Pregabalin Studies			
<i>Adverse Events - 014</i>			
	600 mg/d (%)	150 mg/d (%)	Placebo (%)
Dizziness	37.8	10.1	2.4
Somnolence	22.0	5.1	3.5
Peripheral edema	17.1	3.8	4.7
Asthenia	12.2	3.8	3.5
Weight gain	9.8	2.5	0.0
Amblyopia	8.5	2.5	5.9
Dry mouth	8.5	0.0	2.4
- headache and accidental injury not included			
August 17, 2001		Sharma et al. 2000	

## Pregabalin Studies

### Design - 029

- 338 patients, randomized, double-blind, placebo-controlled



- Power not specified
- Entry
  - Average  $\geq 4$  on 11-point daily Likert during baseline
- Discontinuation due to adverse events:
 

600 mg/d	12.2%
300 mg/d	3.7%
75 mg/d	2.6%
Placebo	3.1%

August 17, 2007

Sharma et al. 2008



**Pregabalin Studies**

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*Outcome Measures - 029*

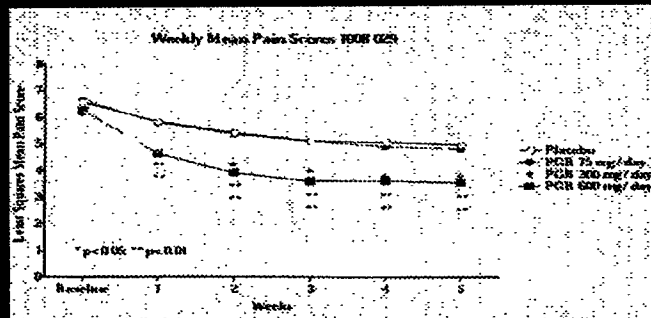
- Primary
  - Weekly mean Likert pain score (probably)
- Secondary
  - Responder rate
  - Patient global impression of change
  - Sleep interference score
  - SFMPQ

August 17, 2004 Sharma et al, 2005

## Pregabalin Studies

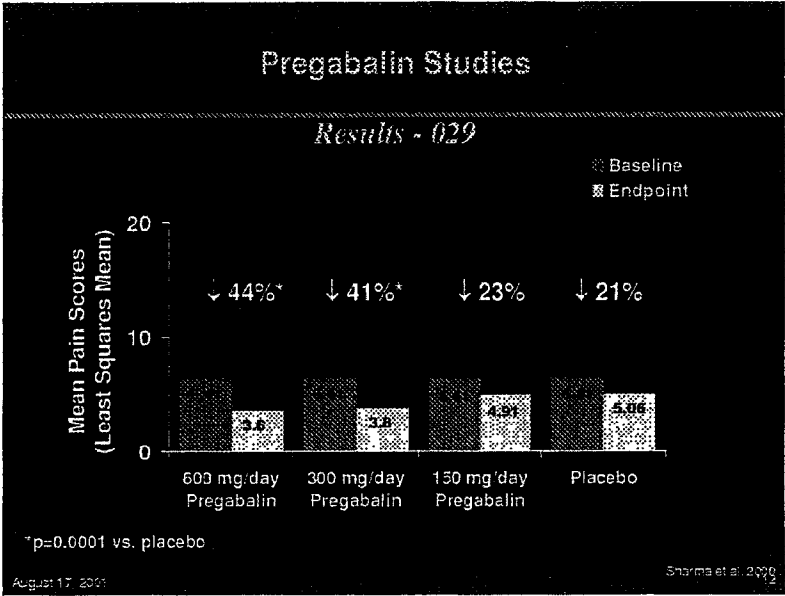
Results - 029

### • Primary



August 17, 2006

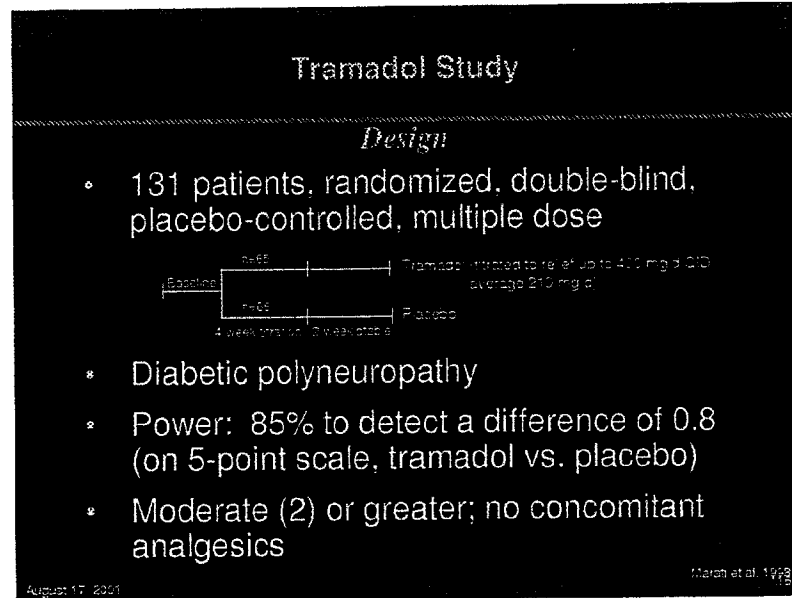
Sharma et al, 2006



Pregabalin Studies	
<i>Responder Rate - 029</i>	
	Responder Rate
600 mg/day	48.1%*
300 mg/day	45.7%*
75 mg/day	22.1%
Placebo	17.5%
Responder = at least 50% reduction in mean baseline pain score	
*p=0.0002 vs. placebo	
August 17, 2001	
Stern et al. 2000	

Pregabalin Studies				
<i>Adverse Events - 029</i>				
	600 mg/d (%)	300 mg/d (%)	75 mg/d (%)	Placebo (%)
Dizziness	39.0	27.2	7.8	5.2
Somnolence	26.8	23.5	3.9	4.1
Peripheral edema	13.4	7.4	3.9	2.1
Amblyopia	8.5	4.9	2.6	1.0
Ataxia	8.5	3.7	6.5	2.1
Confusion	8.5	4.9	0.0	2.1
Constipation	8.5	3.7	0.0	0.0
Headache not included				
August 17, 2006				
Sharma et al. 2003				

Pregabalin Studies	
<i>Responder Rate - 131</i>	
	Responder Rate
300 mg/day	40.0 %*
Placebo	14.5 %
Responder = at least 50% reduction in mean baseline pain score	
*p=0.001 vs. placebo	
August 17, 2001	
Sharma et al. 2000	



**Tramadol Study**

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*Outcome Measures*

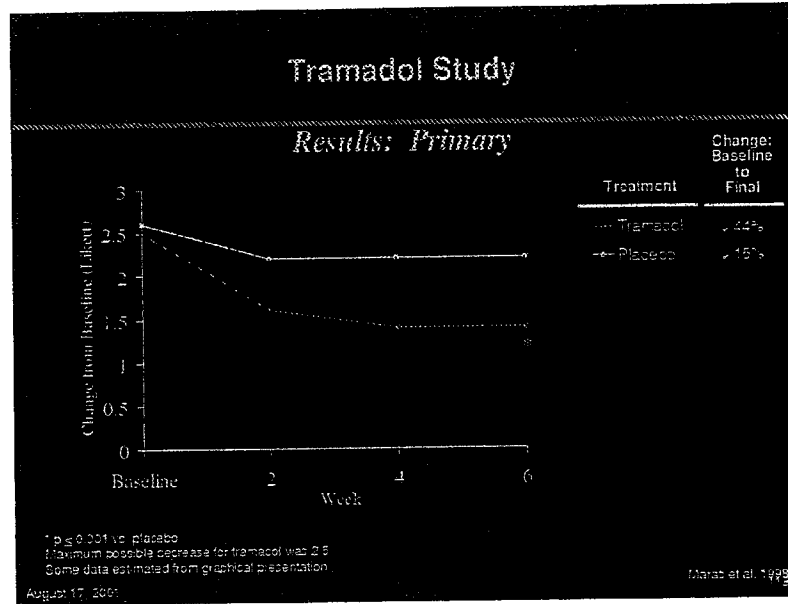
- Primary
  - 5 point Likert pain intensity (at visits)

0	none
1	mild
2	moderate
3	severe
4	extreme
- Secondary
  - Patient rated pain relief score

Complete	4
A lot	3
Moderate	2
Slight	1
None	0
Worse	(-1)
  - Medical Outcome Study measures of daily living activities and sleep

August 17, 2007 Maron et al, 1998

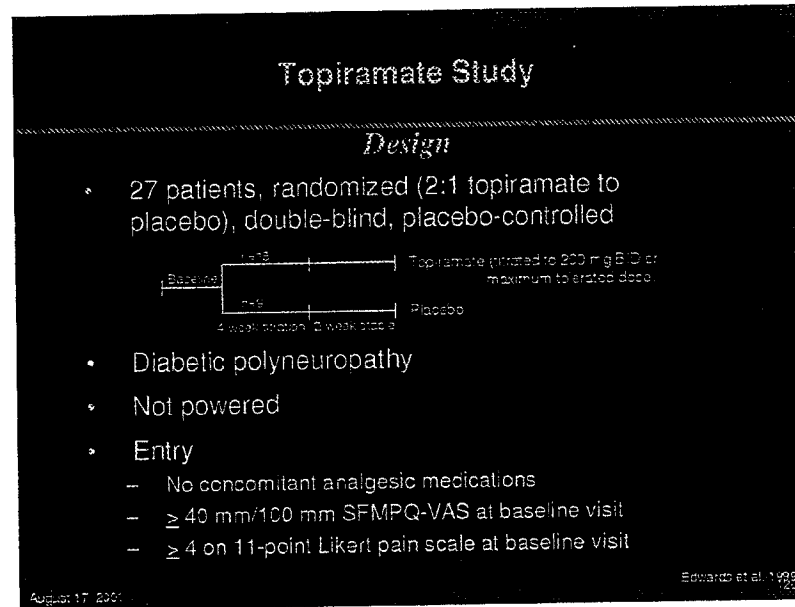




Tramadol Study		
<i>Adverse Events</i>		
	<u>Adverse Event Rate (%)</u>	
	Tramadol	(placebo)
Nausea	23	(3)
Constipation	22	(3)
Somnolence	12	(6)
Dyspepsia	9	(3)
Pruritis	6	(0)
Rash	6	(0)
Vomiting	5	(0)
Fatigue	5	(0)
Dizziness	5	(0)

August 17, 2007

Maran et al. 1998



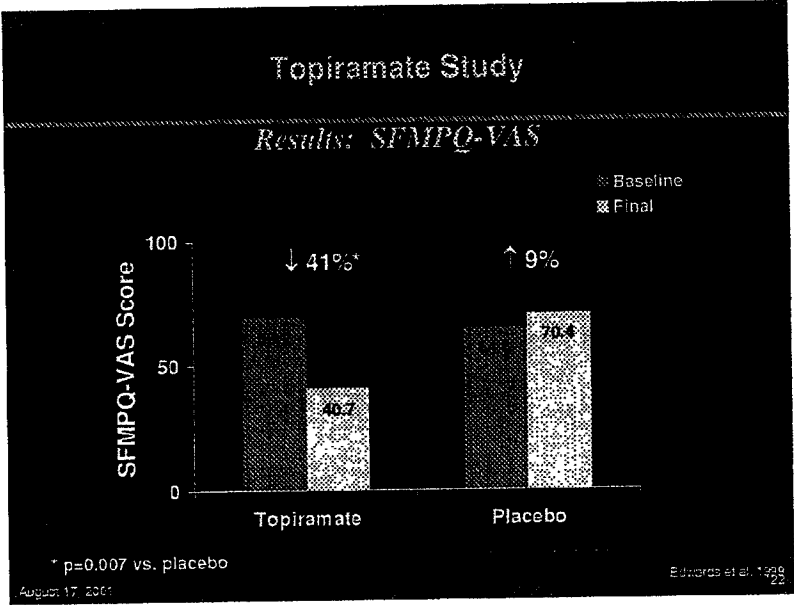
Topiramate Study

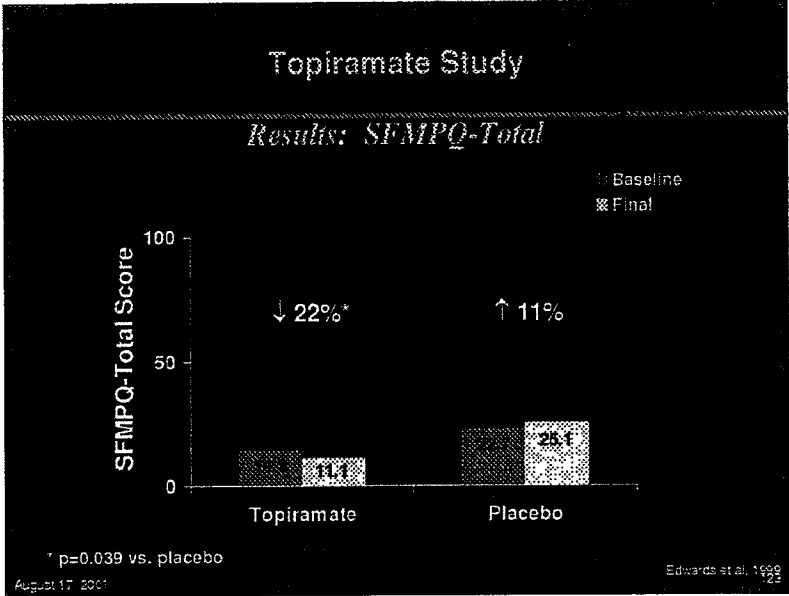
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*Outcome Measures*

- \* Primary
  - SFMPQ-VAS
- \* Secondary
  - SFMPQ-Total
  - Patient global impression of change

August 17, 2001 Edwards et al, 1998





Topiramate Study		
<i>Adverse Events</i>		
	<u>Adverse Event Rate (%)</u>	
	Topiramate	(placebo)
Asthenia	56	(0)
Weight loss of > 10%	22	(0)
Confusion	22	(0)
Paresthesia	17	(0)
Lightheadedness	17	(0)
Dry mouth	17	(0)

August 17, 2004

Edwards et al. 1999

## Amitriptyline for Neuropathic Pain

*Max, 1987*

- Largest (active) placebo-controlled, randomized, double-blind trial of a tricyclic
  - N=29 (completers); 5 discontinued due to AEs
  - 2-week drug-free baseline, 6-week crossover (no washout); 3-week titration, 3-week stable (150 mg)

- Primary endpoint – 13 word verbal description (numeric equivalents)

Placebo	↓ 14%	
Amitriptyline	↓ 51%	(estimated from graph)

- Adverse events

Dry mouth	90%
Sedation	86%
Dizziness	28%
Constipation	14%

August 17, 2007

125



i

***ABT-773 Portfolio Review***  
*December 5, 2000*

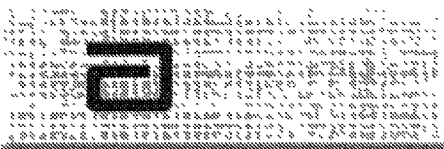
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## *Agenda*

*Part 1: General Overview, Tablet*

- 
- **Introduction-Carl Craft (5 min)**
  - **Executive Summary-George Aynilian (10 min)**
  - **Anti-Infective Market/Commercial Rationale-Rod Mittag (15 min)**
  - **Microbiology-Bob Flamm (20 min)**
  - **Tablet Clinical Program**
    - Phase II data-Joaquin Valdes (20 min)
    - Phase III clinical plan-Joaquin Valdes (10 min)
  - **SPD Summary-Ashok Bhatia (10 min)**
  - **Tablet Key Issues**
    - Analysis of QT/Liver data-Dave Morris (20 min)
    - PK profile-Linda Gustavson (10 min)
    - Regulatory-Jeanne Fox (10 min)
    - Timeline risk George Aynilian (5 min)
  - **Tablet Commercial Profile, Strategy & Financials-Rod Mittag (10 min)**



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## Agenda

Part 2: I.V., Pediatric, Japan, Q&A

- 
- I.V. Program/Issues-Carol Meyer (5 min)
  - Pediatric Program/Issues-Carol Meyer (5 min)
  - Japan Program/Issues-Carol Meyer (5 min)
  - ABT-492 (time permitting)
    - timeline
    - budget
    - rationale
  - Summary-Carl Craft (5 min)
  - Q&A



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**ABT-773**  
*Executive Summary*

---

- **Management**
  - Established European Clinical Team (11 dedicated members)
  - Plans ongoing to strengthen Japan team
  - Completed staffing of Abbott Park team
  - Established communication team
  - Completed conceptual model of study tracking application (web based)
  - Established integrated project management system



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**ABT-773**  
*Executive Summary*

- 
- **Chemistry**
    - Exceeded '00 goals for yield, cost/Kg and deliveries
    - Task Force implemented modification of 3 steps
    - 3 TPMs for intermediates well established
    - Prepared package for justifying Step 5 as starting material



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**ABT-773**  
**Executive Summary**

---

- **Tablet Formulation**
  - Scale up operations at AP and IDC on target
  - Linkage of materials between scales and sites being established by bioequivalency trials.
  - NDA runs and stability were initiated for 08/02 filing.



**ABT-773**  
*Executive Summary*

---

- **IV Formulation**

- Clinical supplies complete. Tox. program ongoing. Phase I planned for 1Q '01.

- **Pediatric formulation**

- Phase I complete with two prototypes. After- taste an issue. Formula optimization required. Pro-drugs under consideration. No funding in '01 plan budget



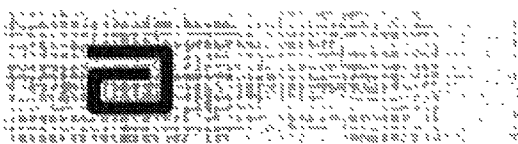
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*Experience Leadership Vision*



**ABT-773**  
*Executive Summary*

---

- **Preclinical Safety**
  - Dog model (IV infusion) and Purkenje fiber studies completed as part of effect of drug on QTc. Additional study planned per EOPll meeting with FDA.
- **Molecular Biology**
  - Extensive work on ribosomal binding completed. Preliminary results published. Additional studies ongoing.

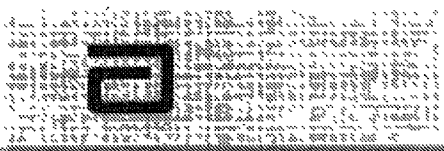


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*Experience Leadership Vision*

**ABT-773**  
**Executive Summary**

---

- **Clinicals**
  - Completed Three Phase IIb studies
  - Decision Support Analysis completed
  - Dose selection 150mg and 150mg bid
  - Initiated Phase III program( 6 studies, 4 under IND)
  - Completed all Investigator's meetings
  - Regulatory meetings
    - UK, Germany, France, US
- **End of Phase II package**
  - Document sent to FDA X/X
  - End of phase II meeting held with FDA 11/26
- **Japan bridging study/Kiko Mtg/Repeat Phase I in Japan**



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**ABT-773**  
*Executive Summary*

---

- **Key Events (Nov '00-June '01)**

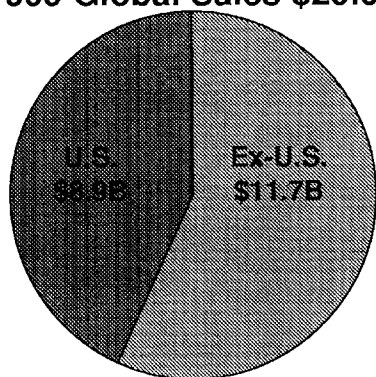
- Initiate Phase III (ABECB, ASP, ABS, CAP) in US/EU
- End of Phase II meeting with FDA (New amendment, informed consent)
- Initiate Japan Phase I program in Japan
- Results of Phase III (CAP/ABS) studies
- Selection of regimen between 150mg QD and 150mg BID for CAP/ABS.
- Set up balance of Phase III studies (CAP/ABS) 4 studies



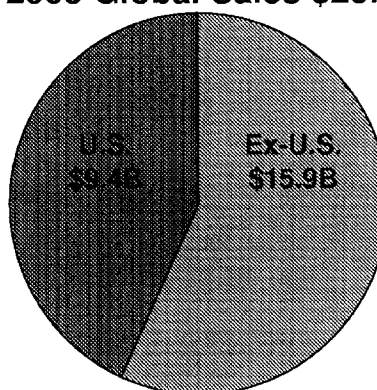
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*Expanding Leadership Vision*

**Global Antibiotic Market Sales**  
*Current vs Future Projection*

**1999 Global Sales \$20.6B**



**2005 Global Sales \$25.3B**



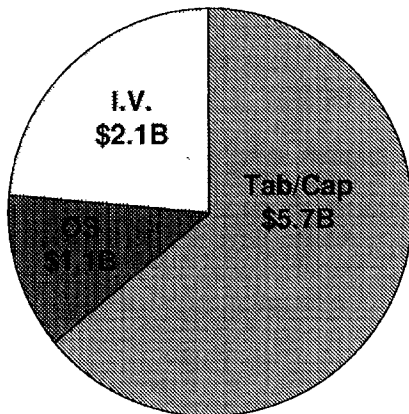
The antibiotic market is a large market and is expected to expand on a global sales basis



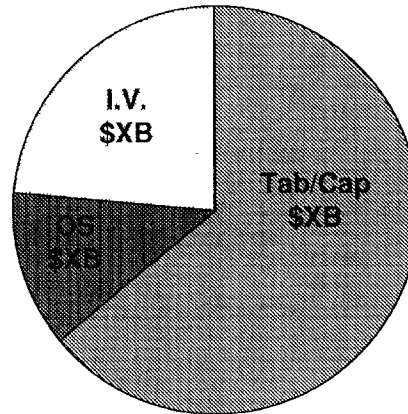
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*Experience. Leadership. Vision.*

**Global Antibiotic Market Sales**  
*by Formulation*

**1999 U.S. Sales \$8.9B**



**1999 Ex-U.S. Sales \$11.7B**



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## Key Competitors

## U.S. Market

	Franchise	Macrolides	Quinolones	Beta-Lactams	Other	Injectables*
Abbott	\$956	\$740		\$48	\$3	\$165
Pfizer	\$1,366	\$1,076	\$71	\$3	\$3	\$213
SB	\$1,303			\$1,229		\$74
Bayer	\$1,034		\$911		\$1	\$122
J&J	\$797		\$612			\$185
Roche	\$526				\$10	\$516
Glaxo	\$551		\$6	\$425	\$28	\$92
BMS	\$387		\$1	\$386		
Lilly	\$107			\$33		\$74
Others	\$1,670	\$95	\$27	\$631	\$298	\$619
'99 Total	\$8,790	\$1,911	\$1,628	\$2,755	\$343	\$2,153
'98 Total	\$7,570	\$1,592	\$1,331	\$2,453	\$272	\$1,922
% Chg	16.12%	20.04%	22.31%	12.31%	26.10%	12.02%
TY vs LY						
* Includes IV form of all classes Source: IMS						

## Ex-U.S. Market

	Franchise	Macrolides	Quinolones	Beta-Lactam	Injectables	Other
Abbott	\$ 717	\$679	\$ 22	\$ 3	\$ 13	\$0
Shionoi Seiyaku	\$ 969	\$ 2	\$ 3	\$ 432	\$ 466	\$ 66
Pfizer	\$ 664	\$267	\$ 12	\$ 68	\$ 245	\$ 71
SKB	\$ 842	\$ 0	\$ 0	\$ 780	\$ 61	\$ 0
BMS	\$ 547	\$ 0	\$ 2	\$ 378	\$ 154	\$ 13
Roche	\$ 460	\$ 0	\$ 3	\$ 43	\$ 303	\$112
Bayer	\$ 524	\$ 0	\$437	\$ 43	\$ 43	\$ 1
Lilly	\$ 437	\$ 28	\$ 0	\$ 337	\$ 66	\$ 6
Fujisawa Yakuhin	\$ 522	\$ 0	\$ 0	\$ 411	\$ 111	\$ 0
Danichi Seiyaku	\$ 497	\$ 0	\$497	\$ 0	\$ 0	\$ 0
'99 Sub-total	\$6,178	\$977	\$976	\$2,495	\$1,461	\$269

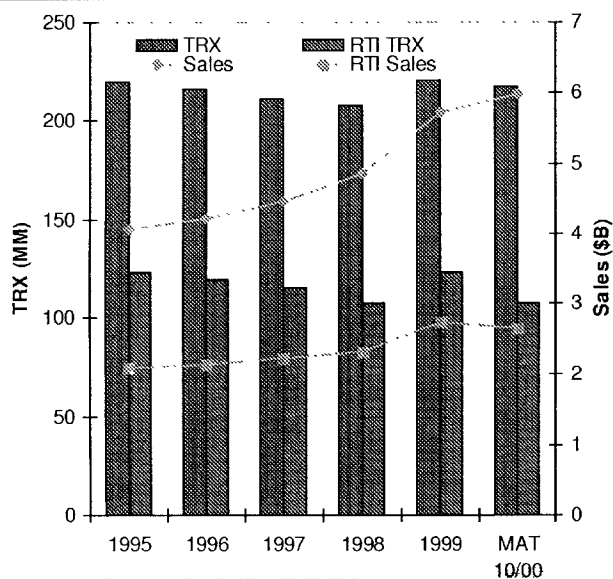


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**Anti-Infectives**

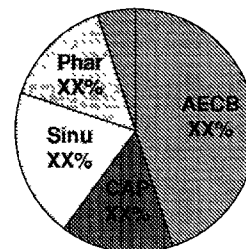
*Experience Leadership Values*

### U.S. Tab/Cap Antibiotic Market TRX & Sales Trends



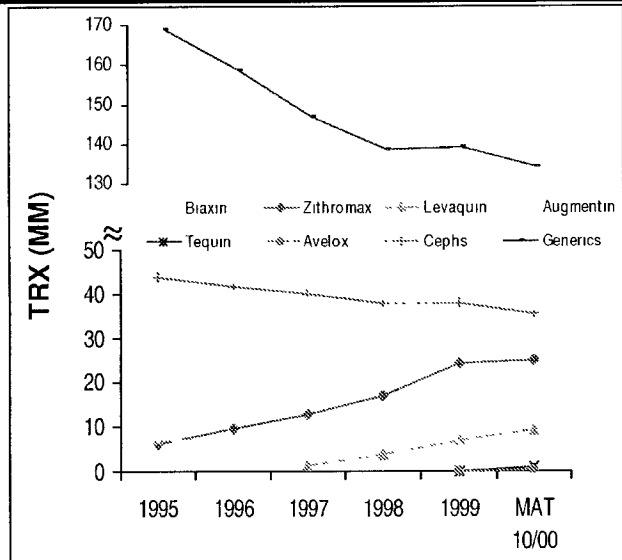
- While negative pressure exists on antibiotic usage, market sales have increased substantially
- TRX CAGR<sub>95-99</sub> = + 0.1%
- Sales CAGR<sub>95-99</sub> = + 8.9%

#### RTI Sales by Indication

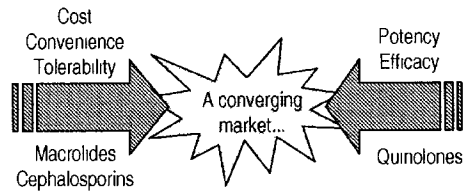


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### U.S. Tab/Cap Antibiotic Market Product Trends



- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Zithromax has driven market demand for cost/convenience/tolerability
- Quinolones (Levaquin, Tequin, Avelox) are fastest growing segment, playing into resistance concerns; 1998-99 growth of 15% (TRX) & 22% (\$)



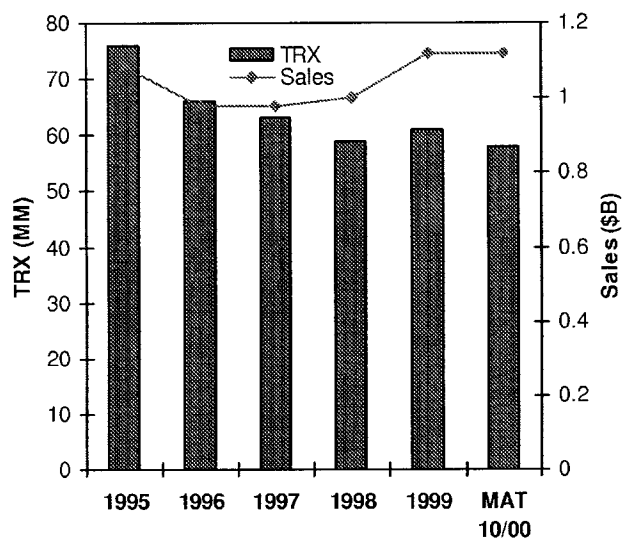
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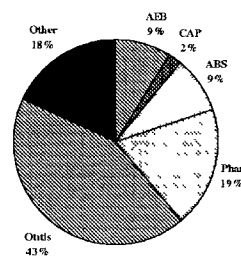


### U.S. Pediatric Antibiotic Market TRX & Sales Trends



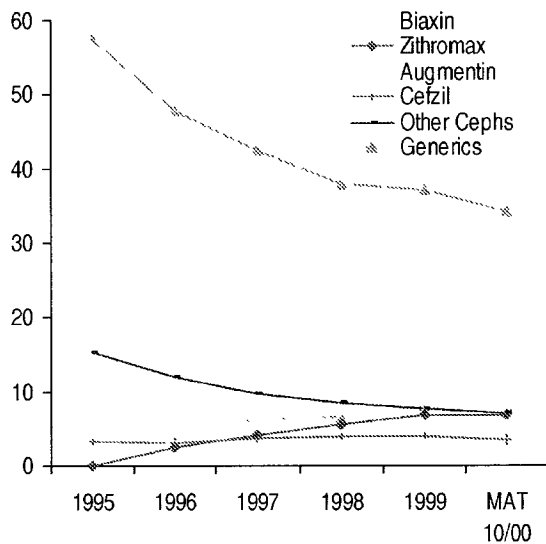
- TRX CAGR<sub>95-99</sub> = - 5.4%
- Sales CAGR<sub>95-99</sub> = + 1.0%
- TRX under greater pressure than Tab/Cap market
- Recent leveling in sales

Sales by Indication



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### ***U.S. Pediatric Antibiotic Market Product Trends***

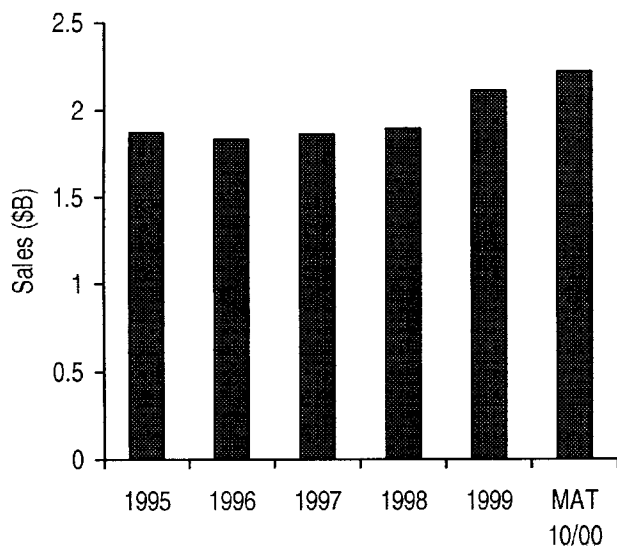


- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Taste and convenience are key market drivers
- Key branded products (Zithromax, Cefzil) lose patent exclusivity in 2005 timeframe
- May be opportunity for ABT-773, as resistance is substantial in this population; also conveys positive "safety" image to brand



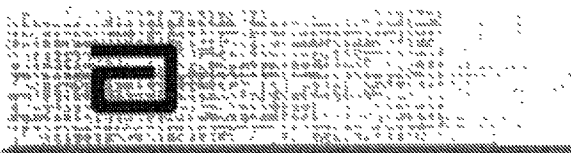
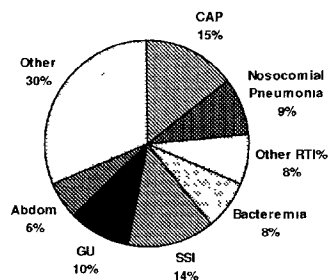
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## U.S. Injectable Antibiotic Market Sales Trends



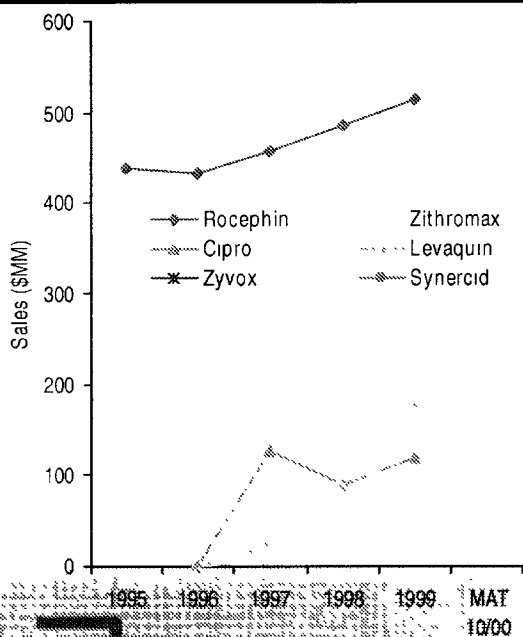
- Current Market: \$2.1B, CAGR = + 3.2%
- Two market segments:
  - Severe community-acquired
    - Rocephin, Levaquin, Tequin, Zithromax
  - Nosocomial
    - Synercid, Zyvox, vancomycin

Uses by Indication



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### ***U.S. Injectable Antibiotic Market Product Trends***



- Rocephin is market leader, quinolones as class are making good gains
- Availability of I.V. has spill-over effect on tablet business
  - direct sales from step-down
  - enhances image of potency
  - more compelling package to managed care



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## **Global Market Drivers**

### ***Negative vs Positive Drivers***

- Antibiotic Resistance

Increasing sensitivity toward “appropriate use” may have negative impact on usage ↓

Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

- Patent Expirations

May increase price sensitivity and bargaining power of MCOs ↓

Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑

- Market expansion ex-US ↑

- Unmet Need ↓

- Overall unmet need relatively low

- Cost, convenience, tolerability take on added importance

- Increasing use of “implied efficacy” metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

- Competition ↓

- 5 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox

- Continued discovery/development activity by key competitors

- High level of promotional activity

Negative driver ↓

Positive driver ↑



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- 
- Resistance surveillance



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ABBT205108

**Patent Expirations**  
*Expiration & At Risk Sales*

	<u>Year</u>	<u>1999 U.S. Sales</u> <u>(\$MM)</u>
Ceftin	2003	\$425
Cipro	2003	\$1,023
Biaxin	2005	\$756
Cefzil	2005	\$357
Levaquin	2005	\$708
Zithromax	2005	\$1,111

\$5,540

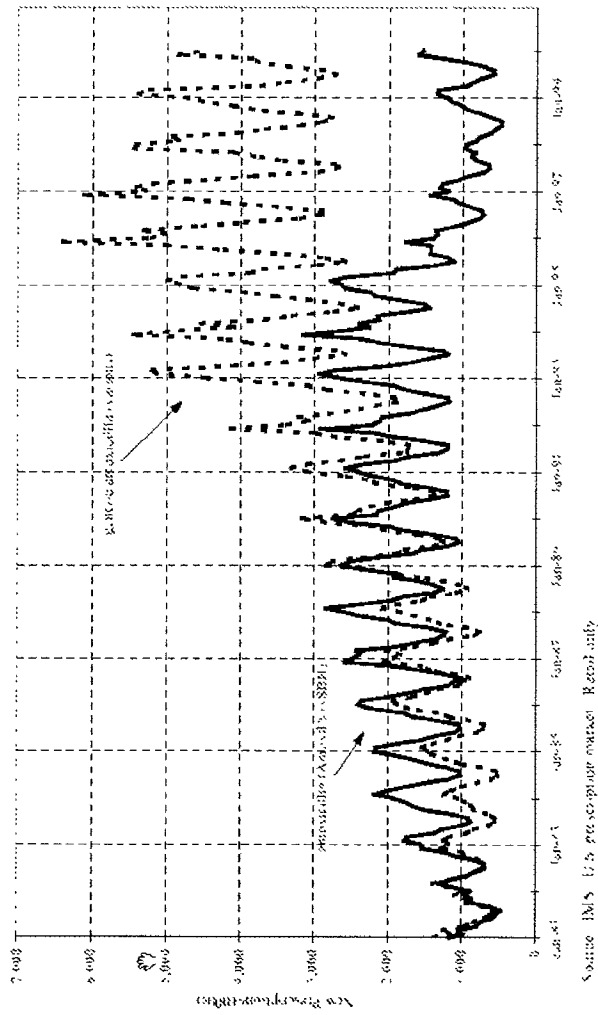


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ABBT205109

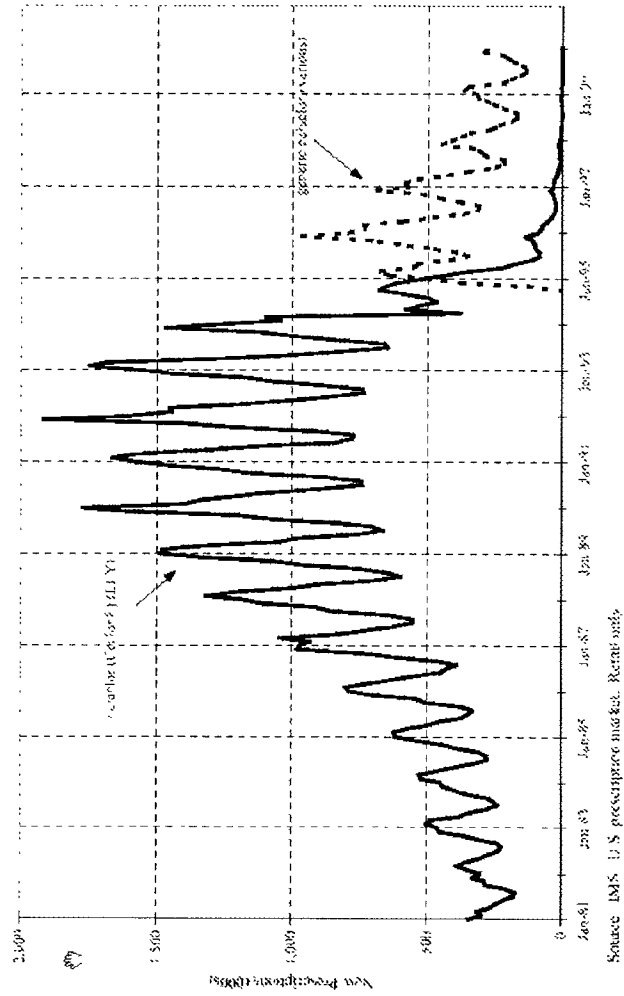
Figure 139. SBH's Amoxil® vs. generic amoxicillin, 1981-2000 (New Prescriptions, monthly data)



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Expenditure Leadership Vision



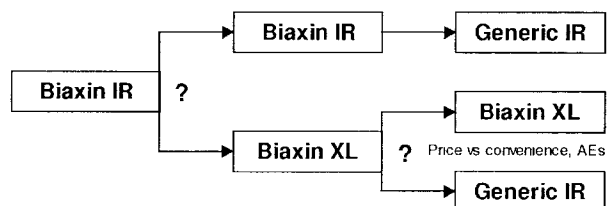
Figure 140. Lilly's Declor® vs. generic declor®, 1981-2000 (New Prescriptions, monthly data)



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*Expedient Endorsing Vision*



### Biaxin Patent Expiration Biaxin/773 Scenarios



		XL==> Generic Conversion		
		Low	Med	High
IR ==> XL Conversion	Low	?	C	C
	Med		?	C
	High			?

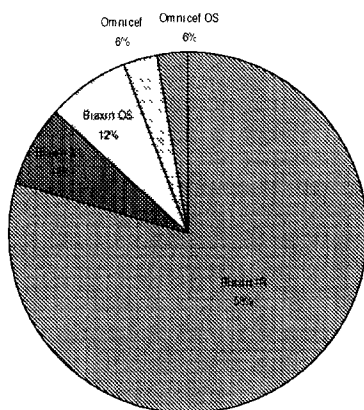
C = Convert Biaxin to ABT-773  
Assumes high conversion rate of IR  
to generics



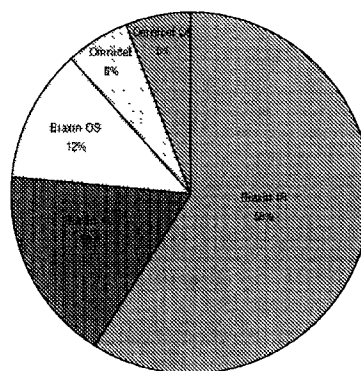
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**Anti-Infectives**  
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## Abbott Anti-Infective Franchise 2001 Plan

U.S. Sales = \$794 MM



Ex-U.S. Sales = \$XXX MM

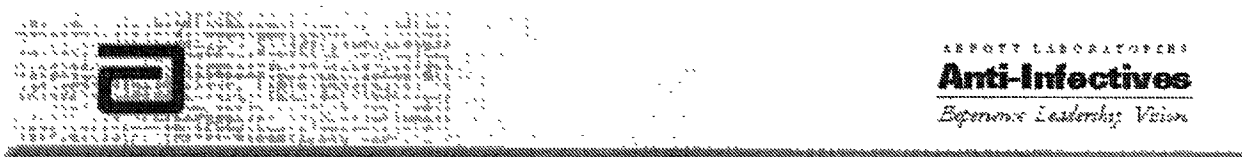


**The global Anti-Infective portfolio is heavily dependent upon Biaxin; ABT-773 represents a key program given the Biaxin patent expiration in 2005**



**ABT-773 Profile**

	Current Profile
Dosing	150 mg QD x 5 d for ABECB & pharyngitis (1-pack) 150 mg QD or BID x 10 d for CAP & ABS (2-pack if QD)
Efficacy	ABECB: 87% Cure, 86% Eradication (150 mg QD) ABS: 89% Cure, 77% Eradication (150 mg QD) CAP: XX% Cure, XX% Eradication (300 mg QD) Pharyngitis: No clinical data, need > 85% for indication
Adverse Events (150 mg QD)	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%
Resistance Claim	Being pursued, dependent on resistance prevalence/recovery/efficacy & availability of I.V.



**ABT-773 Profile**  
vs Biaxin XL

	ABT-773	Biaxin XL
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: 6% Diarrhea: 6% Nausea: 3% Vomiting: 1%
Resistance Claim	Being pursued	Under exploration



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## ***Key Commercial Challenges***

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- **150 mg QD vs 150 mg BID**
  - 150 mg QD may prove efficacious in CAP/ABS ==> uniform QD dosing; however, limited 150 mg QD data currently exists, hence risk of BID dosing for CAP/ABS
  - Even if 150 mg QD efficacious, this regimen could receive regulatory challenge, particularly among ex-U.S. agencies==> QD and BID development programs, increased cost
- **PK**
  - Negative implications for efficacy as well as resistance development
- **H. flu eradication**
  - dose-defining pathogen, limited number of data points to date
  - a strength of quinolones
- **Tolerability may be sub-optimal**
  - diarrhea and taste perversion
- **2nd to market ketolide**
  - Aventis ketolide Ketek (telithromycin), FDA advisory 1/29



**Phase II Data: 150 mg QD vs 300 mg QD**

			Phase IIb Data: Intent-to-treat							
			Bronchitis		CAP		Sinusitis		Total	
Clinical Cure	150 mg QD		85%	104/123	-	-	82%	72/88	83%	176/211
	300 mg QD		83%	107/129	84%	80/95	80%	72/90	82%	159/314
Bacteriological Cure	<i>H. flu</i>	150 mg QD	89%	17/19	-	-	60%	3/5	83%	20/24
		300 mg QD	81%	17/21	100%	9/9	100%	7/7	89%	33/37
	<i>S. pneumo</i>	150 mg QD	77%	10/13	-	-	100%	3/3	81%	13/16
		300 mg QD	90%	9/10	82%	14/17	100%	8/8	89%	31/35



***Ketek Summary***  
***Regulatory Status***

---

- Ketek (telithromycin, Aventis) will be first-to-market ketolide
- U.S.
  - Filed with FDA March 2000
  - **FDA advisory 1/29**
  - Expected approval 1Q01
- Ex-U.S.
  - Package submitted to EMEA as centralized filing in March 2000
    - Rapporteur = Sweden
    - Co-rapporteur = Portugal
    - Expected approval 1Q01
- Phase II in Japan (source: IMS World R&D Focus)



ABBT205118  
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## **Ketek Summary**

### **Profile Summary**

- 
- 800 mg QD for all indications
  - AECB (5 d), CAP (7-10d), sinusitis (5d), pharyngitis (5d)
  - High rate of diarrhea (10-20%), nausea (10%), but no taste perversion
    - statistically greater diarrhea vs trovafloxacin in phase III study
  - Comparable levels of efficacy to comparators (see appendix for full clinical summary)
    - 74%-95% clinical cure
    - 69%-94% overall eradication
    - H. flu eradication is varied, with two CAP studies having 75% and 78% eradication, an AECB and sinusitis study had H. flu eradication of 88% and 100% respectively
  - Liver function elevation
    - mentioned at ICAAC99, but Aventis claimed no clinically relevant impact at ICAAC2000; a CAP study references a 11.3% incidence of abnormal liver function, though the severity is unknown
  - QTc prolongation: Aventis maintains no clinically relevant impact
  - High COGS based on SPD pricing on intermediate
    - estimated telithromycin bulk drug cost of ~\$6,000/kg at launch vs \$3,000 for 773 at launch
    - may limit pricing flexibility
  - Competitive intelligence suggests 14 penicillin resistant isolates submitted, same number as Levaquin (potential for pen-resistance claim, which Levaquin was granted)
    - eradication rate with these isolates unknown, important factor in FDA decision



**Ketek Summary**  
**ABT-773 Comparison**

	ABT-773	Ketek
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 400 mg QD ABECB: 5 d Phar: 5 d CAP: 7-10 d ABS: 10 d (or 5 d?)
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 86-89% Cure, 69-88% Erad ABS: 76-91% Cure, 86-91% Erad CAP: 91-93% Cure, 86-94% Erad Phar: 93-95% Cure, 84-91% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: Not reported Diarrhea: 10-20% Nausea: 10% Liver, QTc: ???
Resistance Claim	Being pursued	Submitted in NDA



## ***Ketek Summary***

### ***ABT-773 Strengths/Weaknesses***

#### ABT-773 Strengths vs Ketek

- ABT-773 is considerably more potent than telithromycin against:
  - resistant and susceptible strains of *S. pneumo*
  - atypicals
  - *H. flu* (based on in vivo animal models)
- Lower rate of adverse events, particularly diarrhea
- 1 tab per dose vs 2
- Mechanistic advantages
  - faster binding to ribosome, slower release from ribosome, perhaps additional binding site(s)
- Potential for greater pricing flexibility

#### ABT-773 Threats/Issues vs Ketek

- 2nd to market
- Potential for BID dosing in CAP and/or sinusitis
- ABT-773 clinical/safety data at 150 mg QD based on relatively few data points
- PK profile



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## Ketek Summary Clinical Data

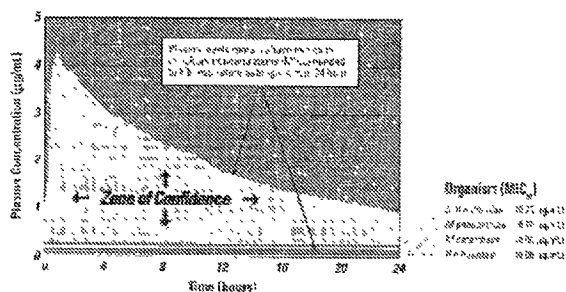
Cure	92%	91%
Embolism	1%	0%
Death	17%	8%
Neutropenia	1%	4%
Discontinuation	5%	1%
<b>Pharyngitis #2</b>	Ketek 800 mg QID x 10 d	Van V 400 mg BID x 10 d
Cure	95%	94%
Embolism	0%	0%
Death	12%	0%
Neutropenia	1%	0%
Discontinuation	0%	0%
<b>CAP #1</b>	Ketek 800 mg QID x 10 d	Amoxicillin 500 mg BID x 10 d
Cure	99%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>CAP #2</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 7-10 d
Cure	91%	95%
Embolism	0%	0%
Death	17% (n=1)	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>CAP #3</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 10 d
Cure	95%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>CAP #4</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 10 d
Cure	95%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>Strains #1</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 10 d
Cure	95%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>Strains #2</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 10 d
Cure	95%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>Strains #3</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 10 d
Cure	95%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%
<b>Strains #4</b>	Ketek 800 mg QID x 7-10 d	Amoxicillin 500 mg QID x 10 d
Cure	95%	97%
Embolism	0%	0%
Death	0%	0%
Neutropenia	0%	0%
Discontinuation	0%	0%

ABBT205122  
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**AVELOX provides a 24-hour Zone of Confidence covering key respiratory pathogens\***

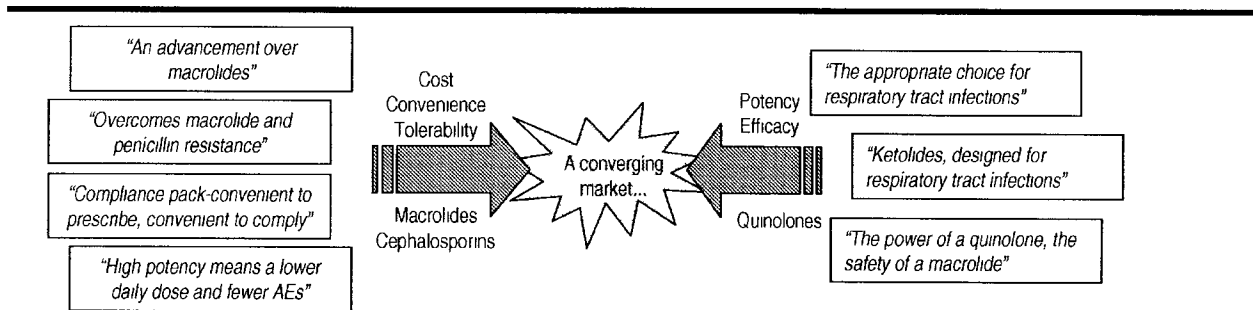
**Steady-state plasma concentrations are well above MIC<sub>90</sub>s of key community respiratory pathogens<sup>1</sup>**

Quinolones are using PK as means of differentiating products-could increase the relevance of PK to prescribers

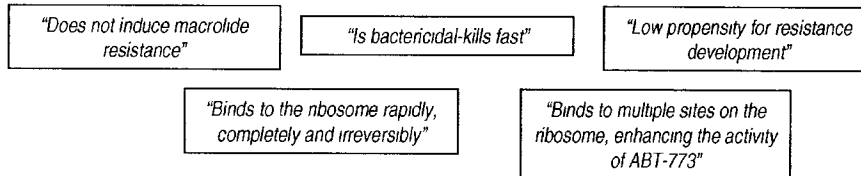


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*Experience Leadership Vision*

## Key Commercial Messages



## Supportive Messages



## ***Communications Strategy***

---

- Messages
  - microbiological data (resistance, the better ketolide)
  - PK (no food effect, favorable drug-drug)
  - Mechanism (ribosome binding, PAE, etc., “explanation” for ketolide activity, defense of dose selection)
  - Clinical data
- Implementation
  - Strategic initiation of studies to support desired messages, monthly strategy meetings, intranet under development to manage activities/history
  - Scientific meetings (51 posters at 6 scientific meetings in 1999-2000)
  - Publications (10 publications in 2000)
  - Medical Liaisons(sp)
  - VIP Visits



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## ICAAC 2000

*International Conference on Antimicrobial Agents and Chemotherapy, Toronto*



See you at ICAAC 2001, in  
Chicago, Illinois!!

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**Forecast Assumptions**

	<u>US</u>	<u>Europe</u>	<u>Japan</u>
Dosing	150 mg QD dosing all indications AECB & Phar, 5 d CAP & ABS, 10 d		
Efficacy	Comparable to other agents		
AEs	Comparable to Biaxin XL		
COGS	\$3,000/kg at launch		
AWP/Day	\$8.60		



**Forecast**


---

	<u>U.S.</u>	<u>Europe</u>	<u>Japan</u>	<u>ROW</u>	<u>Total</u>
Peak Sales	\$432MM				
Peak TRX Share	7.5%				N/A
NPV @12.5%					



# PART 2

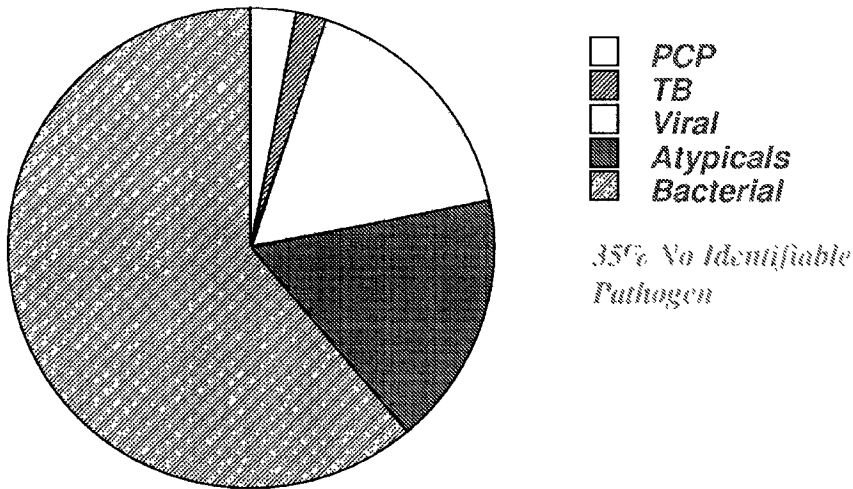
**Microbiology**  
*Overview*

---

- **Ketolides are a Novel Class of Antimicrobial**
  - Active vs. key respiratory tract infection pathogens to include macrolide resistant streptococci
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development



**Microbiology**  
**Community-Acquired Pneumonia in Adults**



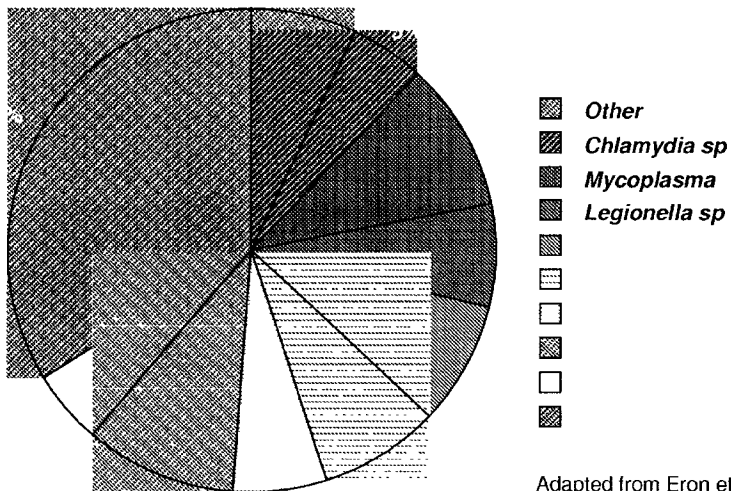
Adapted from Eron et al. Hosp Form 1994;29:122



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*Experiencia. Liderazgo. Vision.*

**Microbiology**  
***Bacterial Causes of Community-Acquired Pneumonia in Adults***

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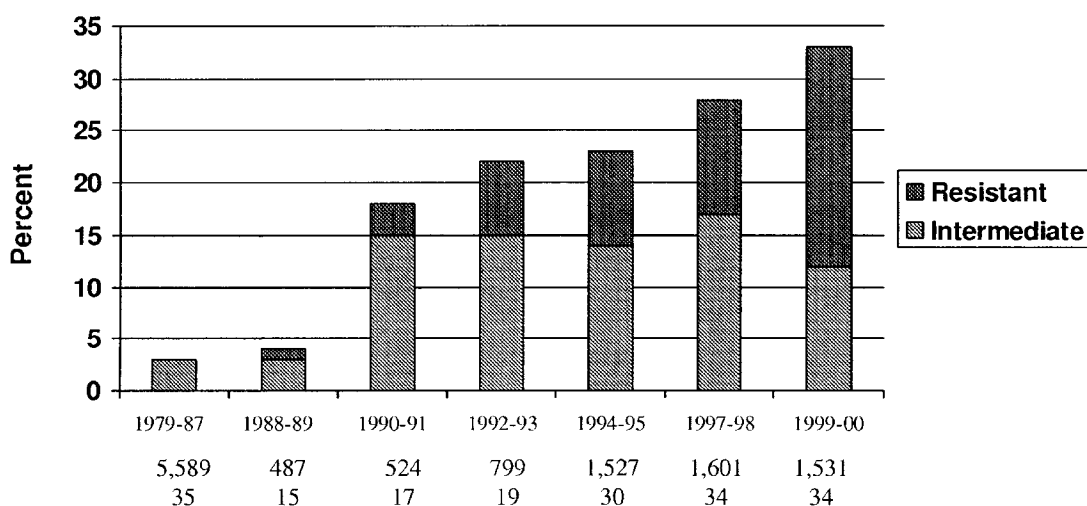
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**Microbiology**

***Penicillin resistance with *Streptococcus pneumoniae* in the United States***



**Microbiology*****US Respiratory Surveillance Studies, Penicillin Susceptibility in *S. pneumoniae****


---

Year	1994-95	1997-98	1999-2000
Season	Winter	Winter	Winter
No. of centers	30	34	34
No. of isolates	1,528	1,601	1531
No. % intermediate	216 (14.1)	278 (17.4)	194(12.7%)
No. % resistant	145 (9.6)	196 (12.2)	29 (21.5%)

Dr. G. Doern, Univ. of Iowa



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ABBT205133



**Microbiology**  
**Antimicrobial Resistance Rates among *S. pneumoniae***

	1994-95	1997-98	1999-2000
Antimicrobial Agent	N=1527	N=1601	N=1531
Macrolide	10.0	18.9	25.9
Tetracycline	7.5	12.9	16.4
Chloramphenicol	4.3	7.2	8.4
Clindamycin	Na	5.6	8.8
TMP/SMX	18.0	20.4	30.3

Dr. G. Doern, Univ. of Iowa



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**Microbiology**

*Rates of Resistance of Non-  $\beta$ -Lactam Antimicrobials with Streptococcus pneumoniae  
Based on Penicillin Susceptibility Category*

Percentage Resistance Among

Antimicrobial	PenS-(n=1,008)	PenI(n=194)	PenR(n=1,531)
Macrolides	5.6	43.3	78.1
Clindamycin	1.4	19.1	25.2
Chloramphenicol	1.0	13.9	27.7
Tetracycline	3.1	32.0	48.0
TMP/SMX	7.6	39.2	94.5

[n=1,531, 34 U.S. centers, 1999-2000], Doern et al



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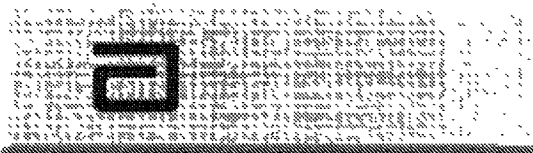
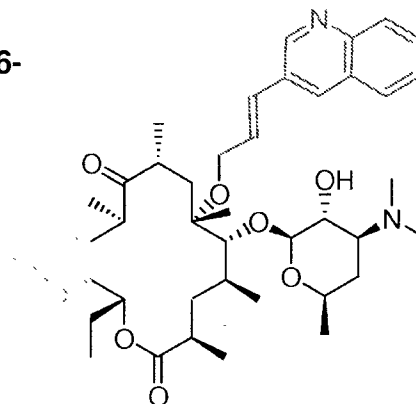
**Microbiology**  
**ABT-773 Structure/SAR**

---

•Quinolylallyl propenyl moiety at the 6-  
0 -position

•Keto group at the 3-position

•Carbamate group at the  
11, 12-position



**ABT-773**

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## **Microbiology**

### **Macrolide Resistance Types**

---

#### **Microbiology Overview**

- **Two major macrolide resistance mechanisms in streptococci and staphylococci:**

- Ribosomal methylase – blocks macrolide binding to target
  - Macrolide and clindamycin MIC >16 µg/mL
- Macrolide efflux – actively pumps macrolide out of cell
  - Macrolide MIC 1-32 µg/mL; clindamycin MIC ≤ 0.25 µg/mL



**Microbiology**

**Resistance Mechanisms Prevalence in *S. pneumoniae* Clinical Isolates**

Genotype	U.S. 1994-95 <sup>1</sup> n=114	U.S. 1997-98 <sup>2</sup> n=302	Canada <sup>3</sup> n=147	Europe <sup>4</sup> n=21	Japan <sup>5</sup> n=62
<b><i>ermB</i></b>	<b>32%</b>	<b>29%</b>	<b>39%</b>	<b>97%</b>	<b>40%</b>
<b><i>mefE</i></b>	<b>61%</b>	<b>71%</b>	<b>56%</b>	<b>3%</b>	<b>43%</b>
<b><i>mef/erm</i></b>	<b>5%</b>	<b>–</b>	<b>&lt;1%</b>	<b>-</b>	<b>16%</b>
<b>Unknown</b>	<b>2%</b>	<b>–</b>	<b>6%</b>	<b>-</b>	<b>0%</b>

<sup>1</sup>Shortridge, et al. *CID*. 1999; 29:1186-8.

<sup>2</sup>Doern, et al. *EID*. 1999; 5(6).

<sup>3</sup>Johnston, et al. *AAC*. 1998; 42:2425-26.

<sup>4</sup>Schmitz et. al. *JAC*. 1999.43:783-92

<sup>5</sup>Nishijima et. al. *JAC*. 1999.43:637-643



**Microbiology****ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Erythromycin MIC**

Drug	Erythromycin MIC $\leq 0.5 \mu\text{g/ml}$ (n=1299)		Erythromycin MIC 1-32 $\mu\text{g/ml}$ (n=222)		Erythromycin MIC $\geq 64 \mu\text{g/ml}$ (n=80)	
	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	$\leq 0.008$	$\leq 0.008 - 0.12$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.5$

1997-1998 Survey, Brueggemann et. al.2000. AAC. 44:447-449



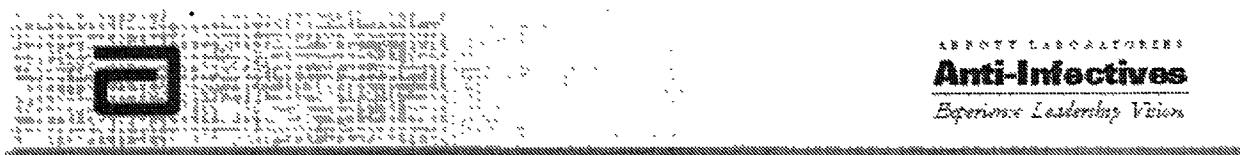
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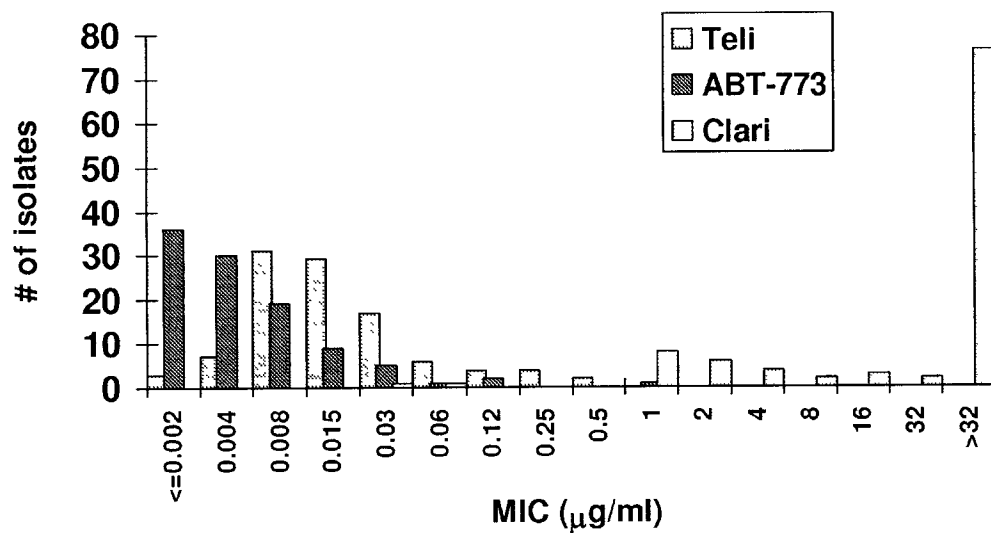
**Microbiology****ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Penicillin MIC**

	Penicillin Susceptible MIC $\leq 0.06$ $\mu\text{g/ml}$ (n=1127)		Penicillin Intermediate MIC 0.12-1.0 $\mu\text{g/ml}$ (n=278)		Penicillin Resistant MIC $\geq 2.0$ $\mu\text{g/ml}$ (n=196)	
Drug	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	$\leq 0.008$	$\leq 0.008 - 0.5$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.25$
Ery	0.06	$\leq 0.03 - >64$	>64	$\leq 0.03 - >64$	>64	$\leq 0.03 - >64$

1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449



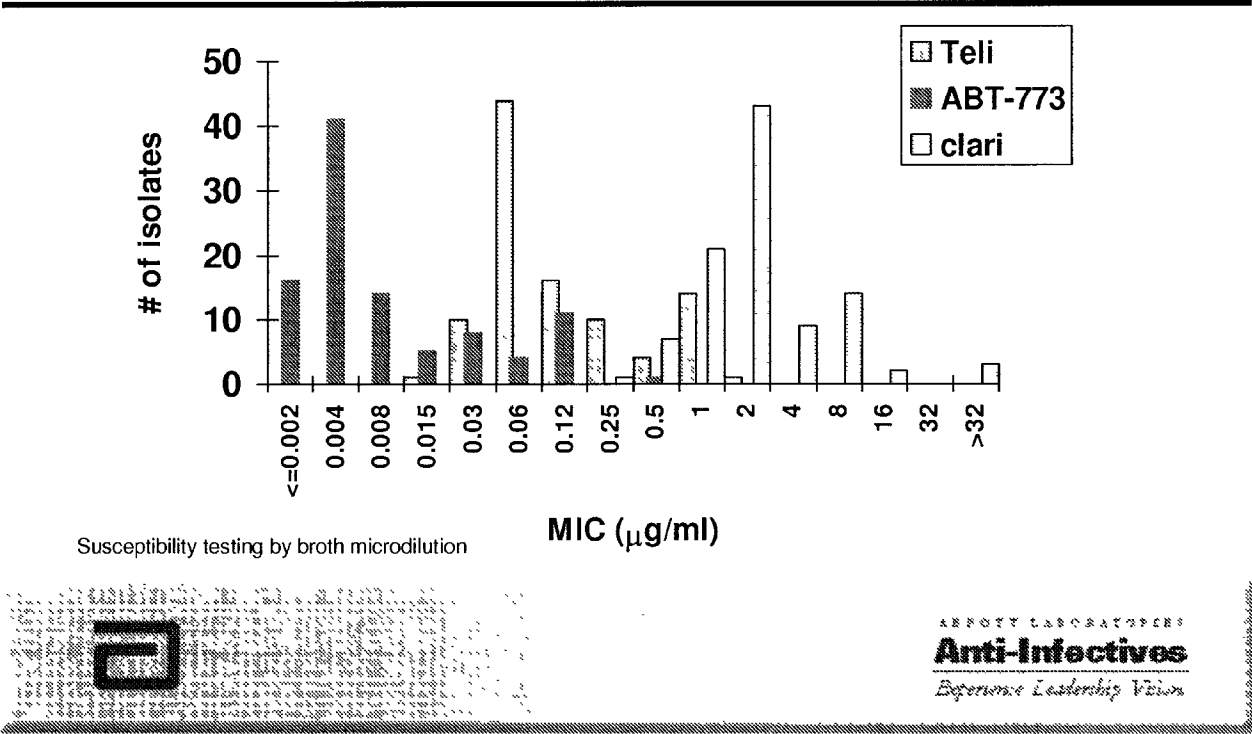
**Microbiology**  
**MIC Distribution of *S. pneumoniae* methylase<sup>+</sup> strains**



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**Microbiology**  
*MIC Distribution of S. pneumoniae efflux<sup>r</sup> strains*



**Microbiology**  
*In vitro Activity, S. pyogenes*

**MIC<sub>90</sub> Range in µg/ml**

Organism	Macrolide susceptible	Macrolide resistant
ABT-773	≤0.016 - 0.03	0.06 - 0.12
Erythromycin	0.06 - 0.12	8 - 16

References:

Barry et al ICAAC 1999 #2144

Dubois et al. ICMASKO 2000 #2.15

Singh et al. ICMASKO 2000 #2.14



**Microbiology***In vitro Activity , Haemophilus, Moraxella spp.***MIC<sub>90</sub> Range in µg/ml**

Organism	<i>H. influenzae</i>	<i>M. catarrhalis</i>
ABT-773	2 - 4	0.06 – 0.25
Azithromycin	2 - 4	0.06 - 0.12
Erythromycin	8 - 16	0.25 - 0.5

## References:

Barry et al ICAAC 1999 #2144

Hoellman et al ICAAC 1999 #2140

Brueggemann et al. 2000.AAC.44:447-449

Shortridge et. al.1999. ICAAC



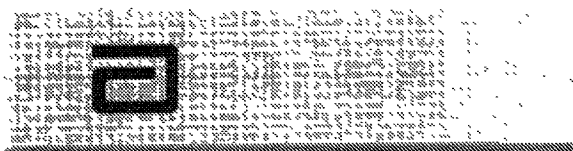
**Microbiology****Comparison of activity vs. respiratory atypical pathogens**MIC<sub>90</sub> in µg/ml

Organism	ABT-773	Ery
<i>Legionella</i> spp. <sup>1</sup> (105)	0.03-0.12	0.25-1.0
<i>M. pneumoniae</i> <sup>2</sup> (18)	≤ 0.0005	0.008
<i>C. pneumoniae</i> <sup>3</sup> (20)	0.015	0.06

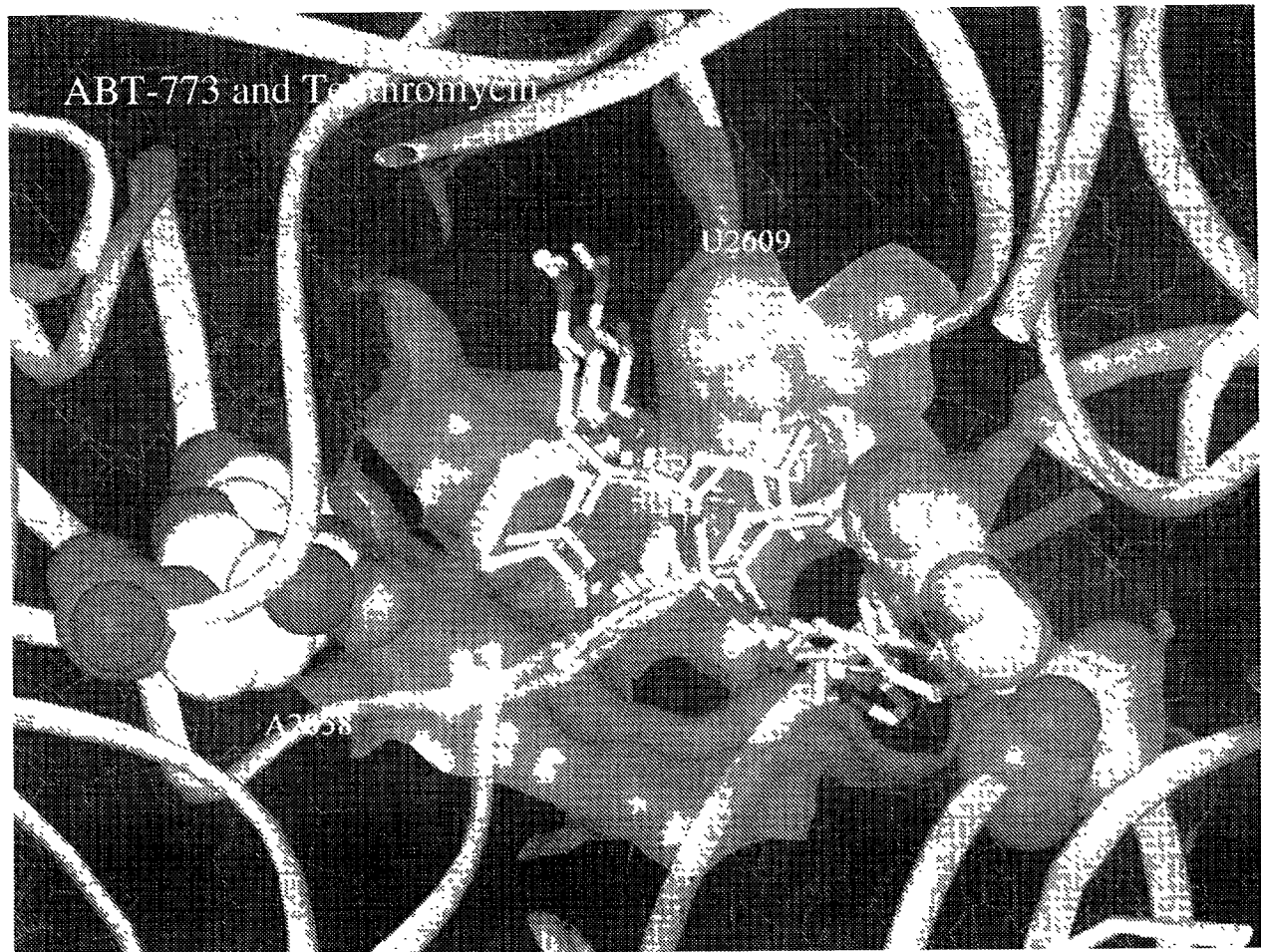
<sup>1</sup>Victor Yu, ICAAC, 2000. Strains tested: *L. pneumophila* serogroup 1 (68), *L. pneumophila* other serogroups (28), *Legionella* spp other than pneumophila (10).

<sup>2</sup>Nilius et al. ECCMID 1999.

<sup>3</sup>Strigl et. al.2000. AAC.44:1112-1113



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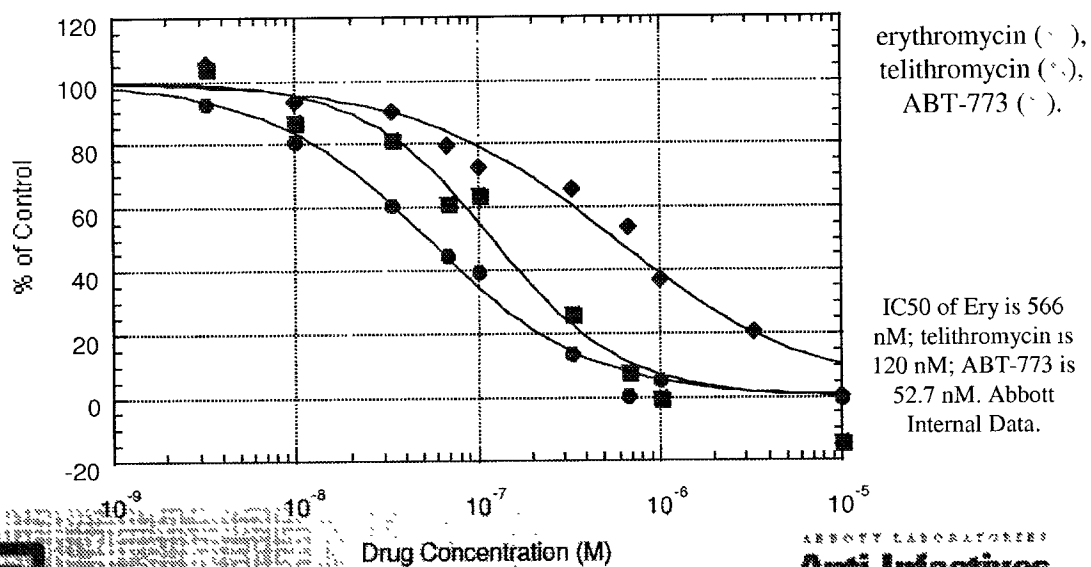


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ABBT205146

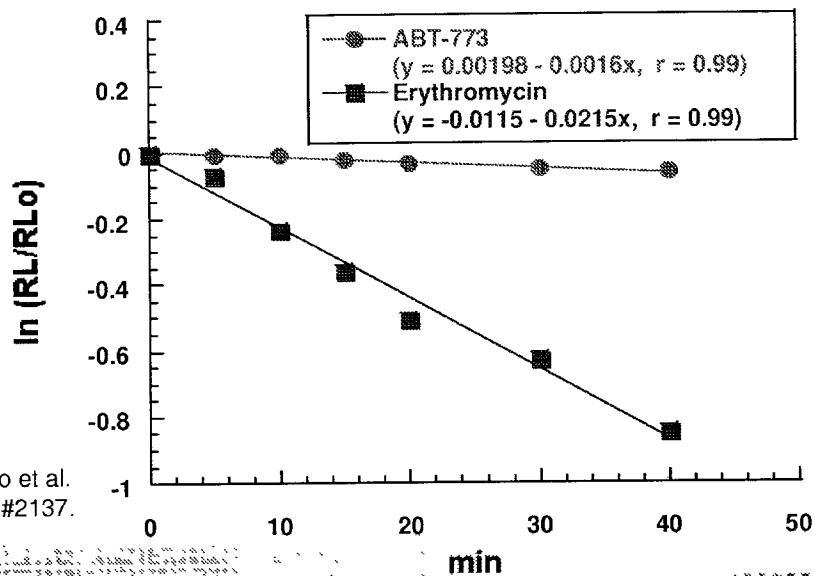
## Microbiology

Ribosome Binding, Susceptible *S. pneumoniae*



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## ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.

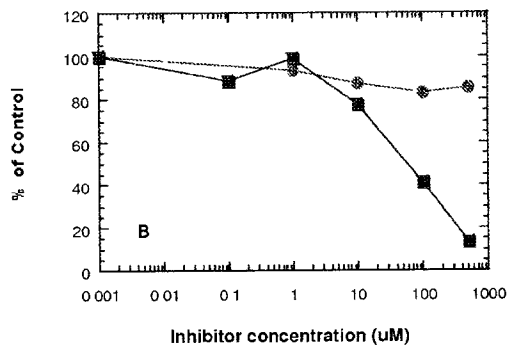
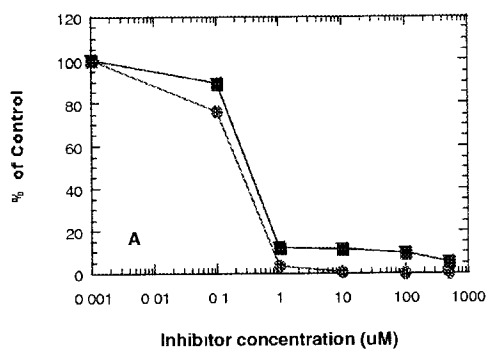


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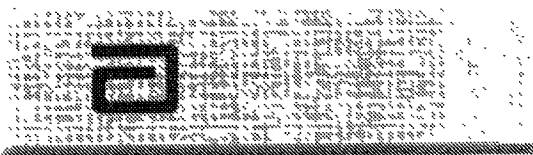
**Microbiology**  
Inhibition of Transcription / Translation

S30 from susceptible *S. pneumoniae*

S30 from resistant *S. pneumoniae*



Red circles: erythromycin  
Blue squares: ABT-773



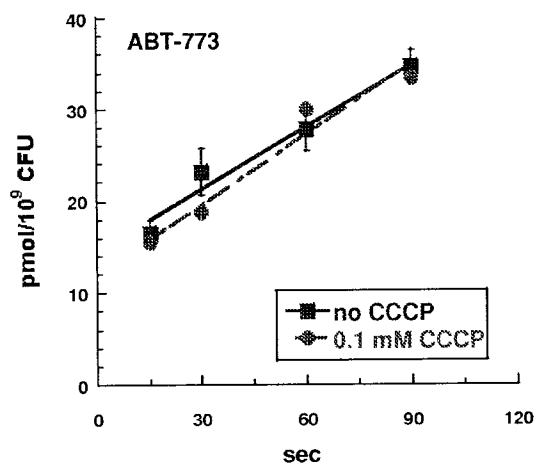
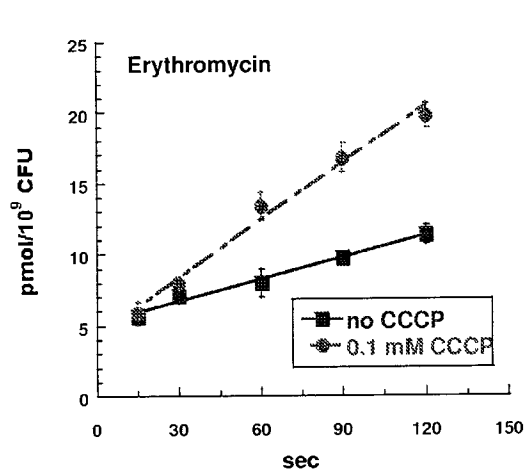
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Z Cao et. al. ICAAC 1999. Poster #2135



## Microbiology

### ABT-773 Accumulation in efflux<sup>+</sup> strain, with and without pump inhibitor (CCCP)



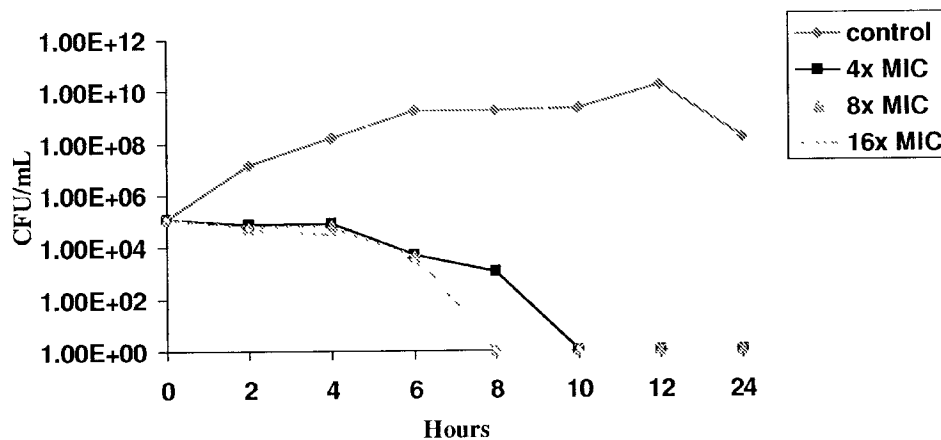
J. Capobianco et al. ICAAC 1999, #2137



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**Microbiology**  
*Bactericidal Activity, S. pneumoniae*

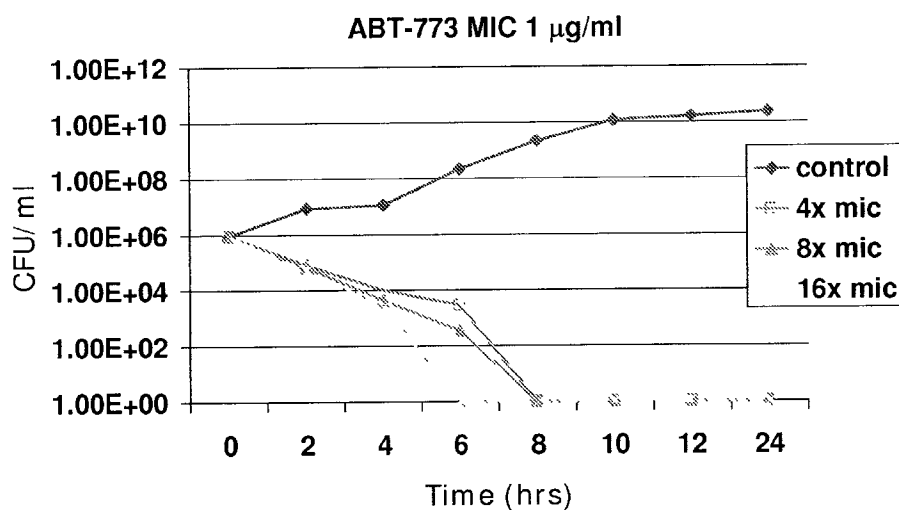
Susceptible *S. pneumoniae*; ABT-773 MIC 0.002 µg/ml



Ramer et al. ICAAC 2000



**Microbiology**  
*Bactericidal Activity, H. influenzae*

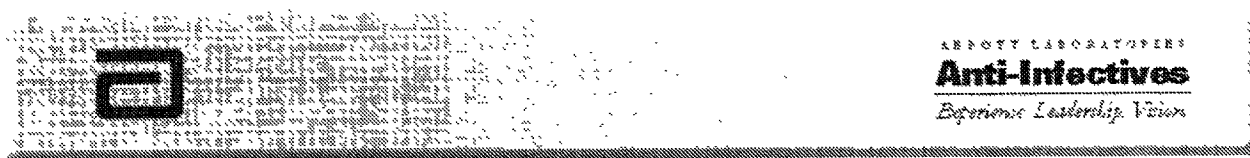


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**Microbiology**  
**Post Antibiotic Effect**

---

- After removal of drug the bacterial growth rate is inhibited
- Justification for dosing regimen such as QD vs. BID
- Addresses resistance development issues
- In vitro
  - *S. pneumoniae*
    - 8 strains
    - mean PAE ABT-773  $\geq$  6.1 hr
    - mean PAE ery 3.8hr
  - *H. influenzae*
    - 5 strains
    - mean PAE ABT-773  $\geq$  6.1 hr
    - mean ery PAE 3.8 hr



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## **Microbiology**

### **Resistance Development**

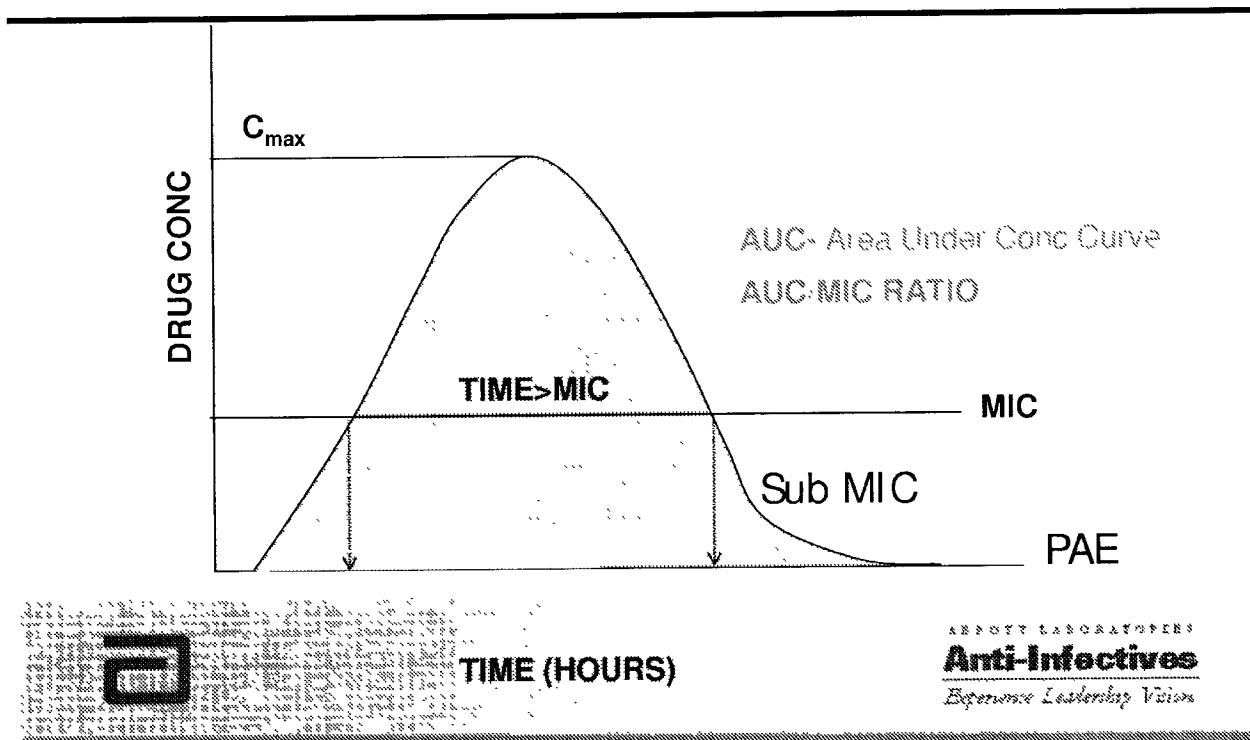
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- **Occur by mutation**
  - Quinolone resistance in GyrA and ParC
- **Acquired from another bacterium**
  - Methylase
  - Efflux
- ***S. pneumoniae***
  - In vitro single step mutation frequency (8XMIC)
    - 1 *S. pneumoniae* (S)  $<5.6 \times 10^{-10}$
    - 1 *S. pneumoniae* *mef*  $<2.6 \times 10^{-12}$
    - 2 *S. pneumoniae* *ermB*  $3.5 \times 10^{-10}$ – $9.4 \times 10^{-11}$
  - Mutation frequency for rifampicin (8XMIC)
    - 4 *S. pneumoniae*  $1.2 \times 10^{-6}$  to  $3.0 \times 10^{-7}$
  - No difference in mutation rate if macrolide resistant or susceptible
  - Low potential for resistance development



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**Microbiology**  
*Pharmacodynamic Parameters*



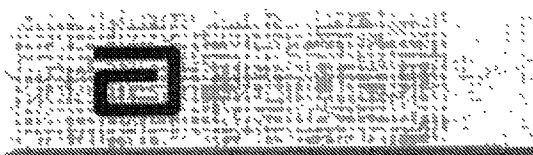
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ABBT205155

**Microbiology**  
*In vivo pharmacodynamics*

---

- **Antibiotic exposure needed for efficacy against *S. pneumoniae* in animal models**
  - AUC/MIC is best predictive parameter for ketolides
  - Rat lung model of pneumonia with *S. pneumoniae*
    - QD an AUC 0-24 ug.h/ml of 0.4-1.0 for an MIC<sub>90</sub> of 0.12
    - BID an AUC 0-24 ug.h/ml of 0.1-0.4 for an MIC<sub>90</sub> of 0.12
  - Lethal mouse model of pneumonia AUC 0-24 of <3-6 ug.h/ml



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**Microbiology**  
*In vivo pharmacodynamics*

---

- **Neutropenic mouse thigh model**

- *S. pneumoniae*
  - 6 macrolide susceptible , 8 macrolide resistant
  - $10^{5.8-7.4}$  CFU/ thigh
  - ABT-773 dose 0.023-24 mg/kg/day Q6 h
  - Net bacteriostatic effect over 24 hrs is measured

Andes, D.R. and W.A. Craig. ICAAC 2000.



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**Microbiology**  
*In vivo pharmacodynamics*

---

- **Neutropenic mouse thigh model- *S. pneumoniae***
  - 24hr AUC/MIC is best PK/PD predictor
  - Prolonged PAEs with concentration dependent killing
    - up to 11 hrs
  - Magnitude of AUC/MIC is not significantly altered by macrolide resistance with strains with MICs as high as 0.5µg/ml

Andes, D.R. and W.A. Craig. ICAAC 2000



**Microbiology**  
*In vivo pharmacodynamics*

---

• **Mouse lethal pneumonia model**

- *S. pneumoniae*-2 strains
  - eryS
  - eryR
- immunocompetent mice
- infected with  $10^{4-5}$  CFU
- treatment 6 or 12 hr post-infection
- subcutaneous dosing
- BID treatment for 3 days

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.

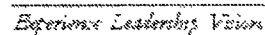


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*Experience Leadership Vision*

### *In vivo pharmacodynamics*

- » infected mouse single dose 12.5 mg/kg- AUC 0-24 ug.h/ml  
3.08+/- 0.32)

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.



**Microbiology**  
*In vivo pharmacodynamics*

---

- Suggests total daily AUC 0-24 ug.h/ml of  $<3-6$  is sufficient for pneumonia
  - ketolide is active vs macrolide resistant strain unlike erythromycin
  - no resistant mutants emerged vs ABT-773 but did for erythromycin

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.

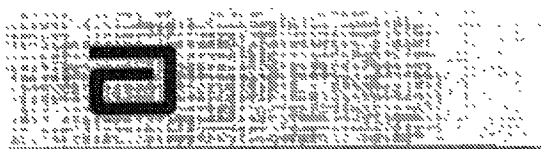


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*Experience. Leadership. Vision.*

**Microbiology**  
*Summary*

---

- Active vs. key respiratory pathogens including macrolide resistant streptococci
- Bactericidal
- Extended PAE
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome
  - Exposure of <1ug.h/ml AUC<sub>24</sub> for mild to moderate pneumonia model and AUC<sub>24</sub> ug.h/ml <3-6 for more severe model



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***Phase II Clinicals***  
*Joaquin Valdes*

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**Phase II Clinicals**  
*Program Summary*

Study	Study Drug Dose/Duration	Patient Numbers/location
M99-048 Phase IIb, Double blind Acute Bacterial Exacerbation of Chronic Bronchitis	ABT-773 150, 300 or 600 mg OD Duration: 5 days	N = 384 US, Germany, France, Italy, Spain, UK, Chile
M99-053 Phase IIb, Double-blind Acute Sinusitis	ABT-773 150, 300, or 600 mg OD Duration: 10 days	N = 292 US, Finland, Greece, Chile
M99-054 Phase IIb, Double-blind Community Acquired Pneumonia	ABT-773 300 or 600 mg OD Duration: 7 days	N = 187 US, Germany, France, Italy, Spain, Poland, South Africa



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***Acute Bacterial Exacerbation of Chronic Bronchitis***  
***M99-048***  
***Clinical Response***

---

	150 mg		300 mg		600 mg	
<b>Clin and Bact. Eval</b>	<b>84%</b>	(42/50)	<b>88%</b>	(49/56)	<b>94%</b>	(59/63)
<b>Clin Eval</b>	<b>87%</b>	(98/113)	<b>90%</b>	(105/117)	<b>90%</b>	(101/112)
<b>ITT</b>	<b>85%</b>	(104/123)	<b>83%</b>	(107/129)	<b>83%</b>	(106/128)





**Acute Bacterial Exacerbation of Chronic Bronchitis**  
**M99-048**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	83% (10/12)	90% (9/10)	100% (13/13)
<i>M. catarrhalis</i>	80% (8/10)	92% (12/13)	91% (10/11)
<i>H. influenzae</i>	94% (17/18)	89% (17/19)	83% (19/23)
Overall	88% (35/40)	91% (38/42)	89% (42/47)



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**Anti-Infectives**  
*Experience. Leadership. Vision.*

**Acute Bacterial Exacerbations of Chronic Bronchitis**  
**M99-048**  
**Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
<b>Taste Perversion</b>	<b>6%</b> (7/126)	<b>19%</b> (25/129)	<b>29%</b> (37/129)
<b>Diarrhea</b>	<b>13%</b> (16/126)	<b>12%</b> (15/129)	<b>21%</b> (27/129)
<b>Nausea</b>	<b>7%</b> (9/126)	<b>13%</b> (17/129)	<b>30%</b> (38/129)
<b>Vomiting</b>	<b>2%</b> (3/126)	<b>3%</b> (4/129)	<b>11%</b> (14/129)
<b>Nausea and Vomiting</b>	<b>0</b>	<b>&lt;1%</b> (1/129)	<b>4%</b> (5/129)
<b>Abdominal Pain</b>	<b>4%</b> (5/126)	<b>4%</b> (5/129)	<b>4%</b> (5/129)



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**Community-Acquired Pneumonia**  
**M99-054**  
**Clinical Response**

	300 mg	600 mg
Clin and Bact. Eval	92% (54/59)	82% (47/57)
Clin Eval	92% (72/78)	80% (56/70)
ITT	84% (80/95)	73% (65/89)



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**Community-Acquired Pneumonia**  
**M99-054**  
**Radiographic Response**

**(Resolution/Improvement)**

	300 mg	600 mg
Clin and Bact. Eval	100% (56/56)	89% (48/54)
Clin Eval	99% (73/74)	88% (57/65)
ITT	84% (80/95)	72% (64/89)



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**Anti-Infectives**  
*Experience Leadership Vision*

**Community-Acquired Pneumonia  
M99-054  
Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	300 mg		600 mg	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)
<i>M. catarrhalis</i>	75%	(6/8)	50%	(2/4)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)
<i>C. pneumoniae</i>	95%	(19/20)	79%	(19/24)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)
Overall	91%	(63/69)	81%	(57/70)



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**Community-Acquired Pneumonia  
M99-054  
Adverse Events**

**All Adverse Events**

	300mg		600mg	
GI and Taste				
Taste Perversion	17%	(16/95)	26%	(24/92)
Diarrhea	14%	(13/95)	19%	(17/92)
Nausea	12%	(11/95)	22%	(20/92)
Vomiting	10%	(9/95)	15%	(14/92)



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***Sinusitis  
M99-053  
Clinical Response***

---

	150 mg	300 mg	600 mg
Clin Eval	89% (70/79)	83% (70/84)	71% (59/83)
ITT	82% (72/88)	80% (72/90)	67% (59/88)

---



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**Sinusitis  
M99-053  
Radiographic Response**

**(Resolution/Improvement)**

	150 mg	300 mg	600 mg
Clin Eval	86% (68/79)	86% (71/83)	78% (59/76)
ITT	81% (71/88)	81% (73/90)	67% (59/88)



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*Experience Leadership Vision*



**Sinusitis**  
**M99-053**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	3/3	8/8	9/12
<i>M. catarrhalis</i>	8/9	3/4	4/4
<i>H. influenzae</i>	3/5	7/7	5/7
<i>S. aureus</i>	1/1	1/1	3/4



**Sinusitis**  
**M99-053**  
**Adverse Events**

**All Adverse Events**

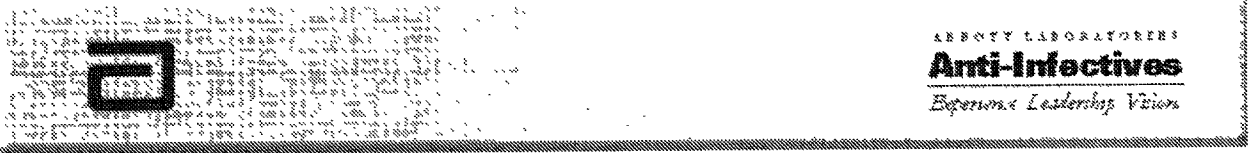
	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
Taste Perversion	1% (1/97)	14% (14/98)	27% (26/97)
Diarrhea	6% (6/97)	6% (6/98)	17% (16/97)
Nausea	3% (3/97)	12% (12/98)	26% (25/97)
Vomiting	1% (1/97)	6% (6/98)	17% (16/97)



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*Insert cure/erad/AE summary table*

---



**ABECB, CAP, AMS**  
**M99-048, M99-054, M99-053**  
**Clinical Response**

---

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

---



**ABECB, CAP, AMS  
M99-048, M99-054, M99-053  
Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	87% (13/15)	91% (30/33)	91% (29/32)
<i>M. catarrhalis</i>	84% (16/19)	84% (21/25)	84% (16/19)
<i>H. influenzae</i>	87% (20/23)	94% (33/35)	77% (37/48)
Overall	86% (49/57)	90% (84/93)	83% (82/99)



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*Experience Leadership Vision*

**ABECB, CAP, AMS**  
**M99-048, M99-054, M99-053**  
**Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
<b>Taste Perversion</b>	<b>4%</b> (8/223)	<b>17%</b> (55/322)	<b>27%</b> (87/318)
<b>Diarrhea</b>	<b>10%</b> (22/223)	<b>11%</b> (34/322)	<b>19%</b> (60/318)
<b>Nausea</b>	<b>5%</b> (12/223)	<b>12%</b> (40/322)	<b>26%</b> (83/318)
<b>Vomiting</b>	<b>2%</b> (4/223)	<b>6%</b> (19/322)	<b>14%</b> (44/318)



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### ***Phase II summary***

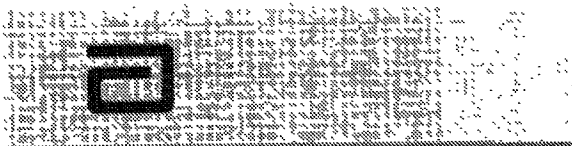
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- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD will be evaluated in comparative studies of ABECB and pharyngitis in phase III
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS



---

***Phase III Clinical Program  
Joaquin Valdes***



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### Proposed Indications and Treatment Duration

Infection	Dosage (QD)	Duration (days)
Pharyngitis/Tonsillitis due to <i>S. pyogenes</i> *	150 mg	5
Acute bacterial sinusitis due to		
<i>H. influenzae</i>	150 mg (or BID)	10
<i>M. catarrhalis</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10
Acute bacterial exacerbation of chronic bronchitis due to		
<i>H. influenzae</i>	150 mg	5
<i>H. parainfluenzae</i>	150 mg	5
<i>M. catarrhalis</i>	150 mg	5
<i>S. pneumoniae</i> **	150 mg	5
Community-acquired pneumonia due to		
<i>C. pneumoniae</i>	150 mg (or BID)	10
<i>H. influenzae</i>	150 mg (or BID)	10
<i>L. pneumophila</i>	150 mg (or BID)	10
<i>M. pneumoniae</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10

\* Including macrolide-resistant strains.  
\*\* Including penicillin-resistant and macrolide-resistant strains.



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*Experience Leadership Vision*

**Phase 3 Studies**

Studies starting in year 2000:

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	260	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	260	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	300	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	250	EU (Non-IND)



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**Phase 3 Studies****Studies starting in year 2000 (Cont.):**

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	600	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	800	US, Canada, EU (IND)



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*Defining Leadership Vision*

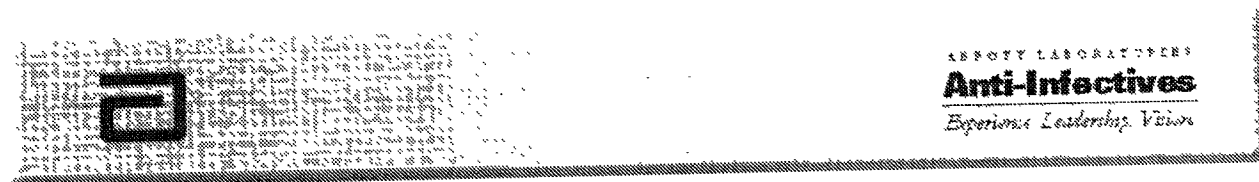
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**Phase 3 Studies**

Studies starting in year 2001:

Study	Indication	Comparator	Number ABT-773 Subjects	Location
M00-221	CAP	Levofloxacin	225	US, Canada (IND)
M00-220	CAP	Augmentin or Amoxicillin	250	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	US, Canada (IND)
M00-218	Sinusitis	Augmentin or Quinolone	250	EU (Non-IND)

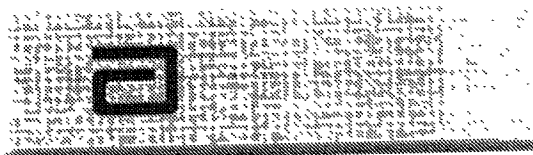


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ABBT205185

### Proposed Claim for Macrolide or Penicillin Resistant Bacteria and Atypicals

Claim	Supporting Data
Macrolide-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Penicillin-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Macrolide-resistant <i>S. pyogenes</i>	15 isolates worldwide from Phase 3 pharyngitis
Atypicals; <i>C. pneumoniae</i> , <i>M. pneumoniae</i> , <i>Legionella spp.</i>	15 isolates worldwide per organism (include positive serology) from Phase 3 CAP



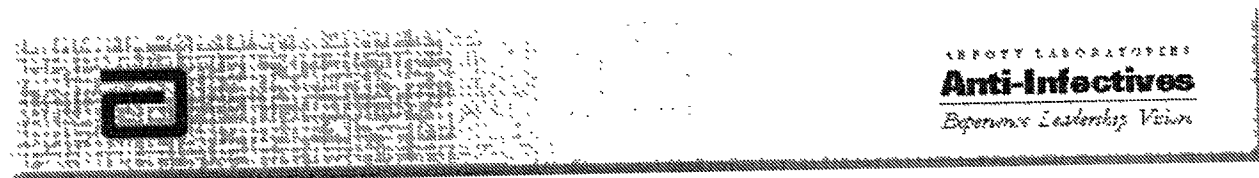
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ABBT205186

**Bulk Drug Manufacturing**  
*Ashok Bhatia*

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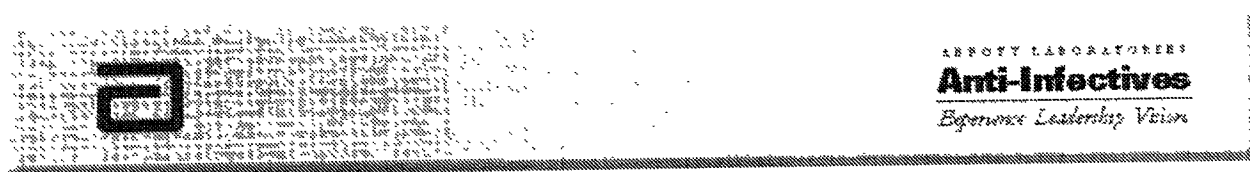
# PART 3

## ***Bulk Drug Manufacturing Agenda***

---

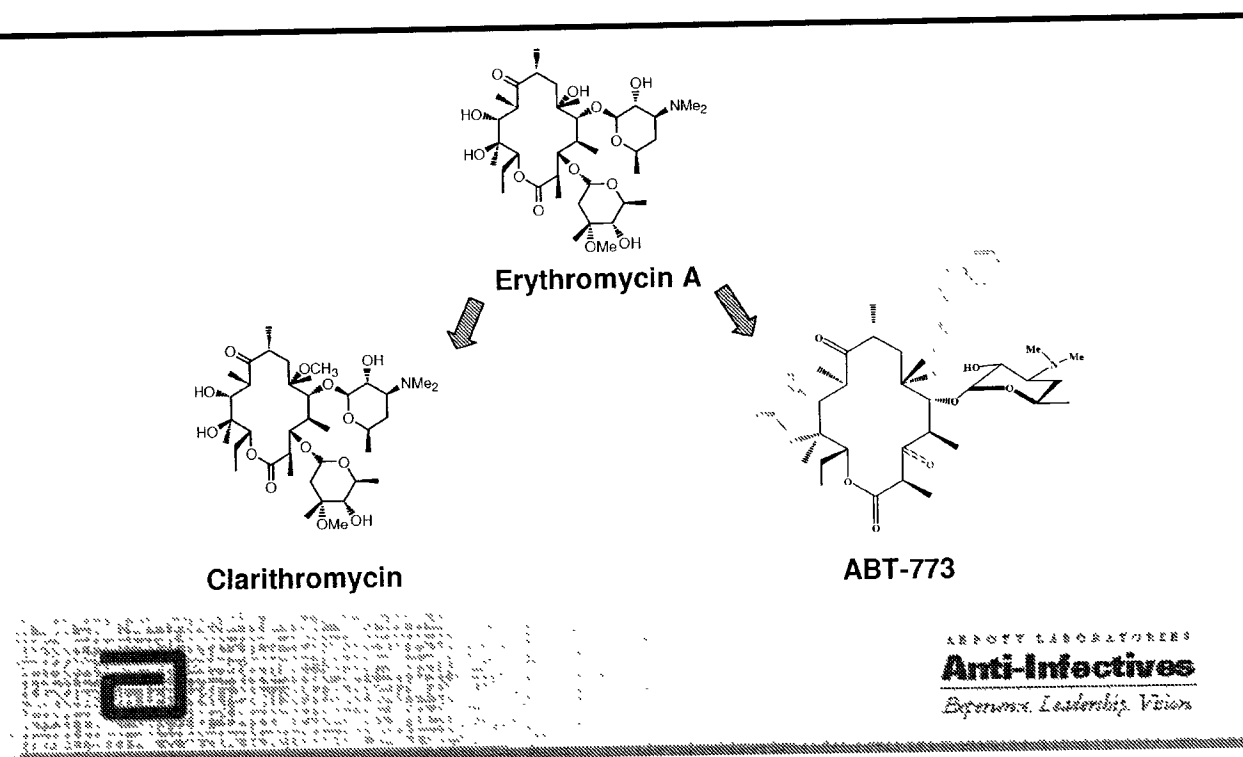
### **Agenda**

- Chemistry
- Process Strategy and Review
- Cost Review and Projection

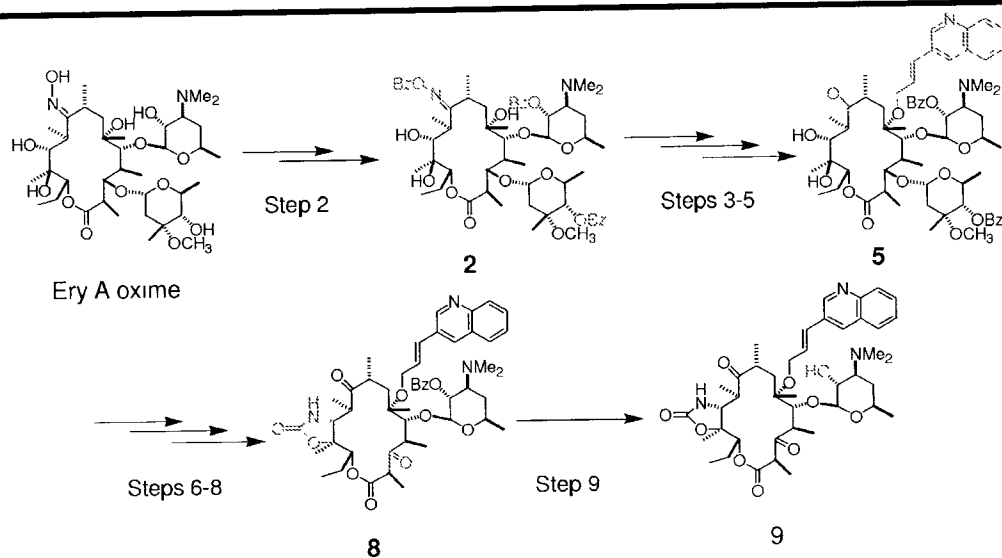




**Bulk Drug Manufacturing**  
**Macrolide Structures**



**Bulk Drug Manufacturing**  
**ABT-773 Synthesis**

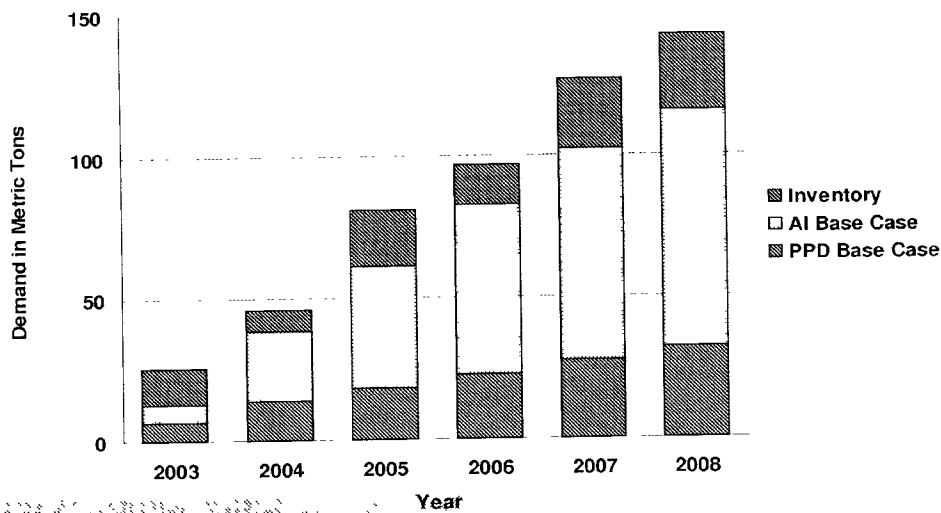


ABT - 773

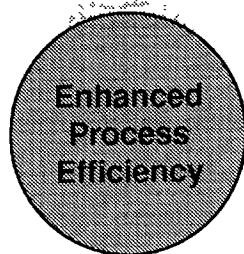
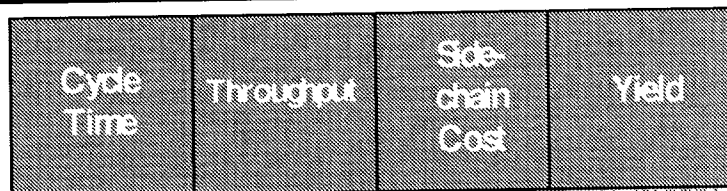
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**Bulk Drug Manufacturing**  
Drug Substance Demand

**ABT-773 Bulk Demand - Consolidated LRP**



ABT-773 LABORATORY RESEARCH  
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**Bulk Drug Manufacturing Process Improvements**

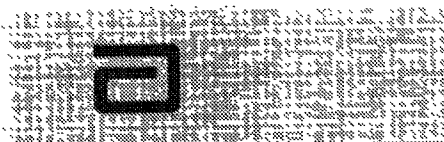
	1998	1999	2000
CycleTime (Days)	53	35	30
Throughput Batch Size	100 kg	175 kg	350 kg
Manuf. Sites	1	5	5
Side-chain Cost	\$2500/kg	\$1100/kg	\$950/kg
Yield (%)	18	21	28



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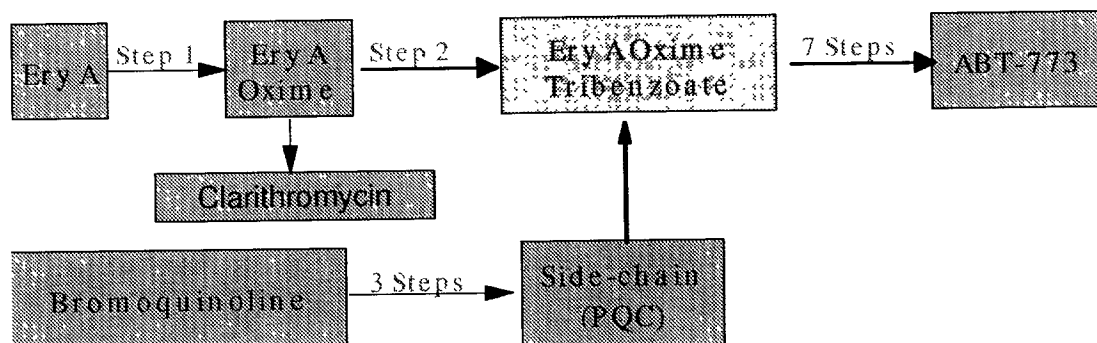
**Bulk Drug Manufacturing**  
*Comparison of Projected & Actual Demand/Cost*

		1999	2000	2001
Bulk Drug	Demand (kg)	1,400	2,520	1,675
	Actual (kg)	1,488	2,815	
Cost/kg	Projected (\$)	\$10,000	\$6,500	\$5,000
	Actual (\$)	\$7,800	\$5,400 (est.)	



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*Experience Leadership Vision*

### Bulk Drug Manufacturing Synthesis

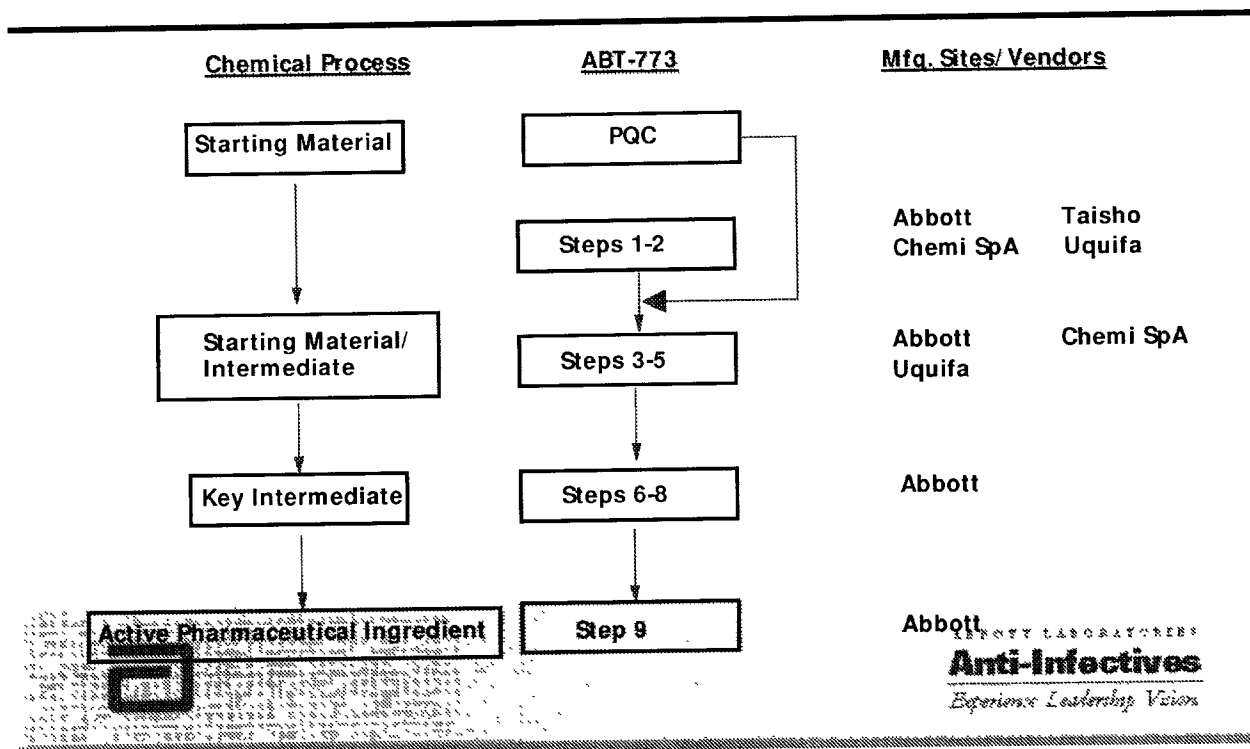


- Bromoquinoline sources from India and China
- Side-chain outsourced from India and Europe
- Intermediates up to Step 5 outsourced/internal



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**Bulk Drug Manufacturing**  
**Manufacturing Strategy: Starting Materials & Intermediates**



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**Bulk Drug Manufacturing**  
*Step 5 as Starting Material*

---

**Criteria:**

- Readily available at commercial scale
- Structure incorporated in Drug Substance molecule
- Well-characterized and known impurity profile
- Prepared by know methods

**Advantages:**

- Commercial flexibility – additional manufacturers
- Process improvements (changes) without FDA prior approval
- Cost advantage

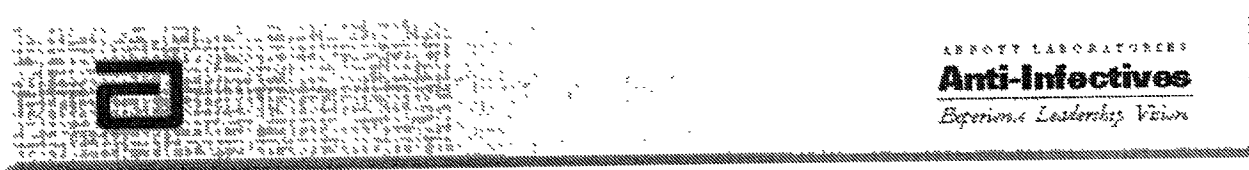
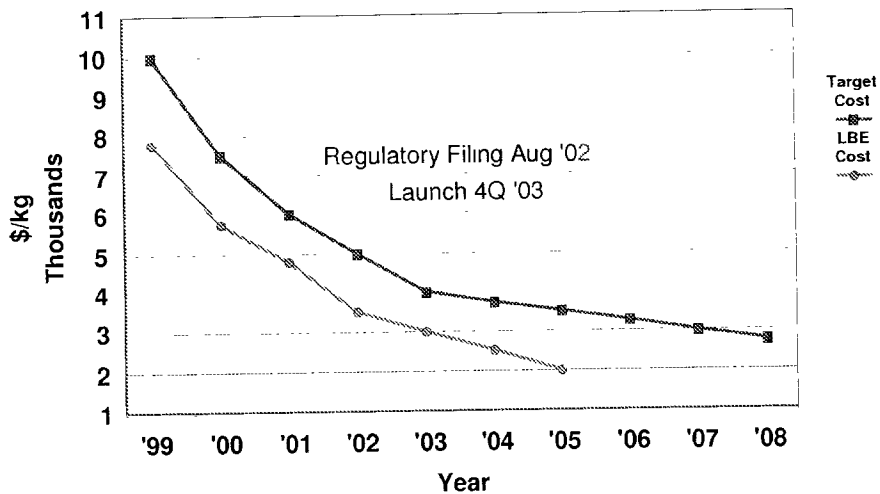




## Bulk Drug Manufacturing

### Projected Bulk Drug Costs

Cost of Goods based on Current Process

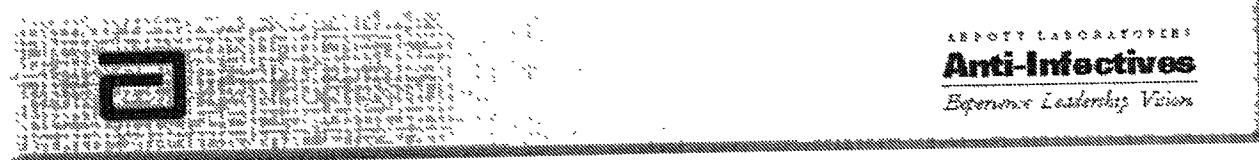


***Bulk Drug Manufacturing***  
*Projected Annual Capacity, Single Site*

---

Bldg C7A/ NC	15MT
Bldgs C17 and C7A/ NC	50MT

Alternative strategies:  
Step 8 at vendor site(s)  
Manufacturing in Abbott, Puerto Rico



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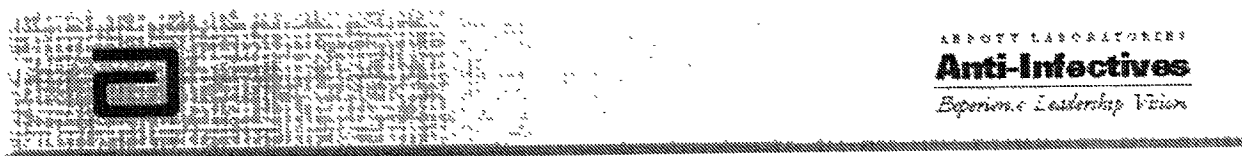
ABBT205198

## ***Bulk Drug Manufacturing Summary***

---

### **Summary**

- A viable process developed for commercial launch
- On track to achieve commercial target cost
- Identified strategies to meet long term bulk substance demand



## ***Tablet Key Issues***

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ABBT205200

**QT Prolongation**  
*Dave Morris*

---



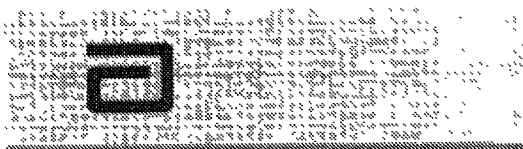
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ABBT205201

### *Summary of ECG*

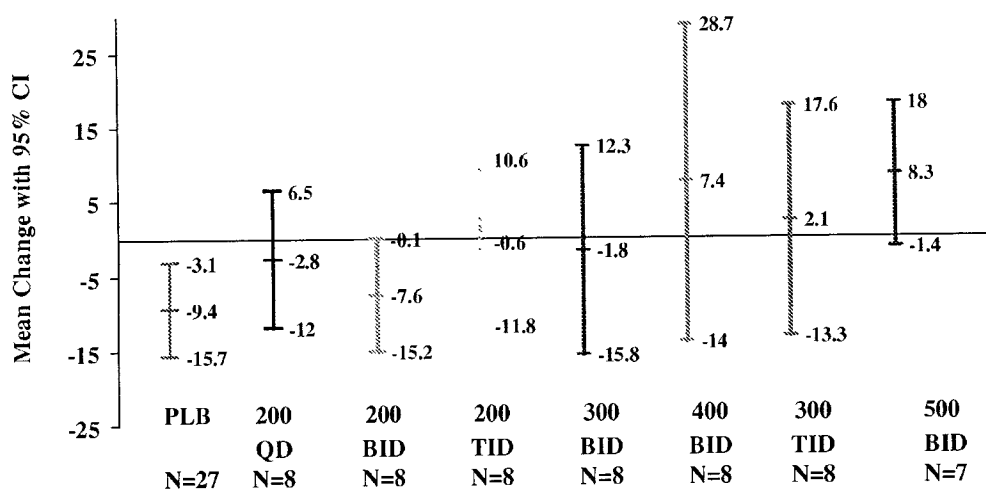
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- A possible dose effect in Phase I at total daily dose  $\geq 800\text{mg}$ .
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole.
- No concentration response in Phase I studies ( $\leq 300\text{mg}$ ).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies.
- Will continue to monitor QT in Phase III programs.



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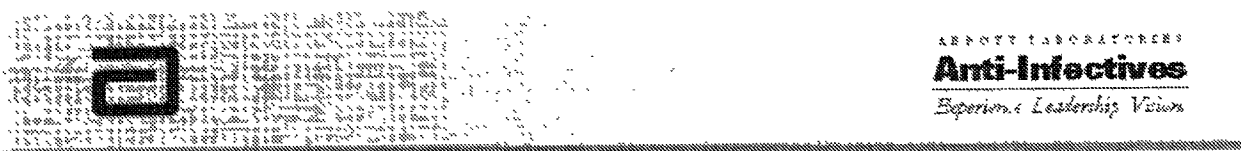
**Mean Change of QTC  
(Multiple Rising Dose Study)**



### ***Multiple Rising Dose Study***

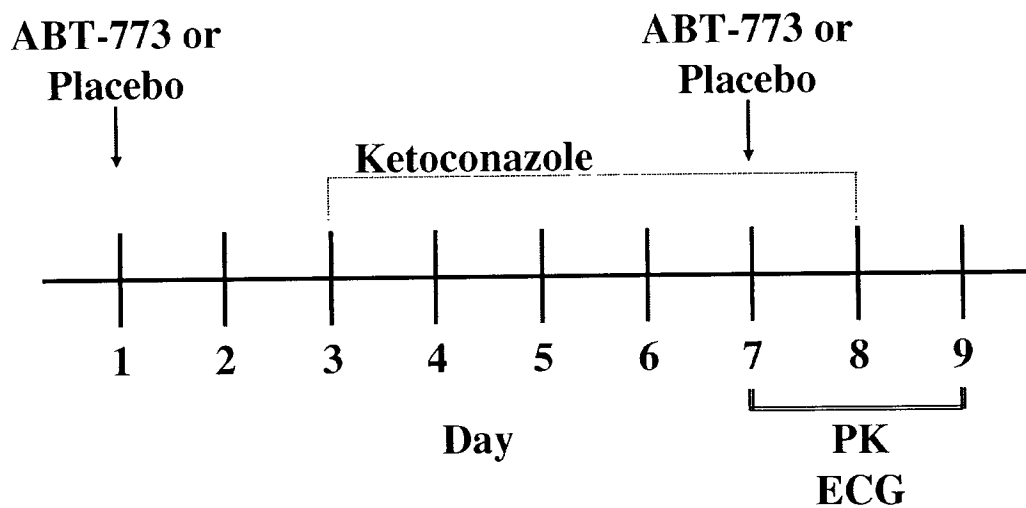
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- No subject had QTc increase > 60 msec
- 3 subjects had QTc increase 30-60 msec ( $\geq 800$ mg/day)
- No subject had QTc of >500 msec
- No syncope observed



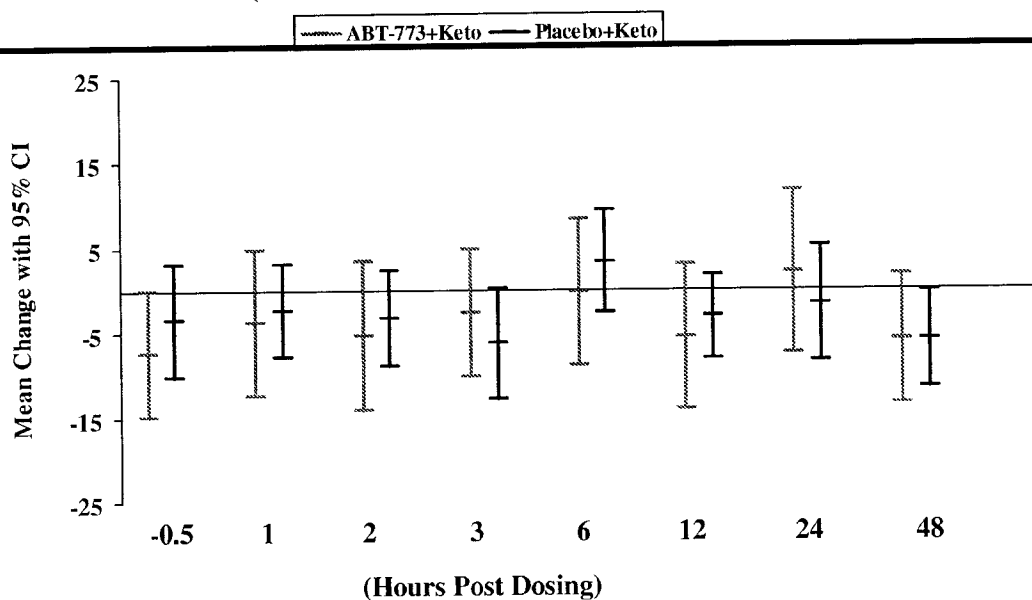


### *Ketoconazole Interaction Study*



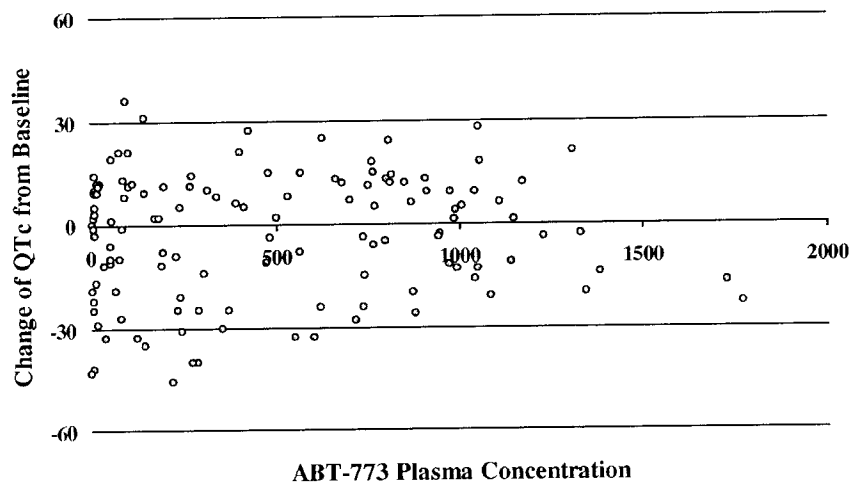
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**Mean Change of QTC**  
**(Ketoconazole Interaction Study - N = 18)**



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### Ketoconazole Interaction Study



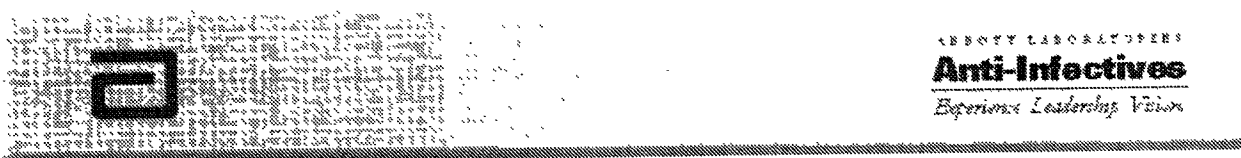
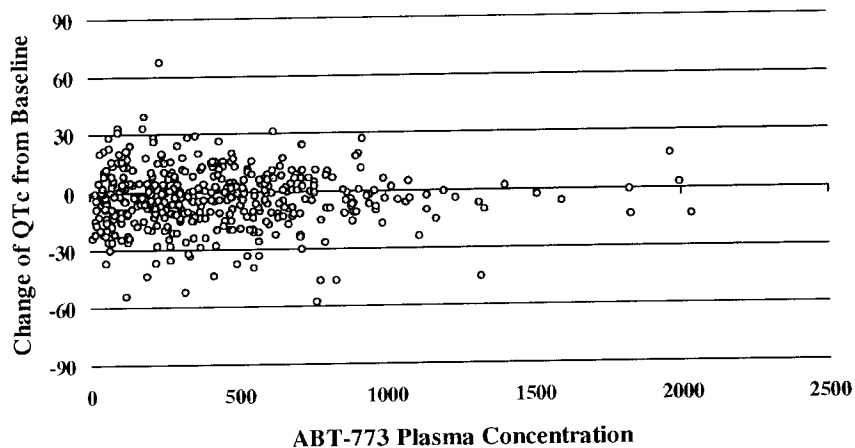
### ***Ketoconazole Interaction Study***

---

- No subject had QTc increase > 60 msec.
- 2 subjects had QTc increase of 30-60 msec.
- No subject had QTc of >500 msec
- No syncope observed



Pooled Multiple Dose Studies  
( $\leq 300\text{mg/day}$ )



### ***All Phase I Studies***

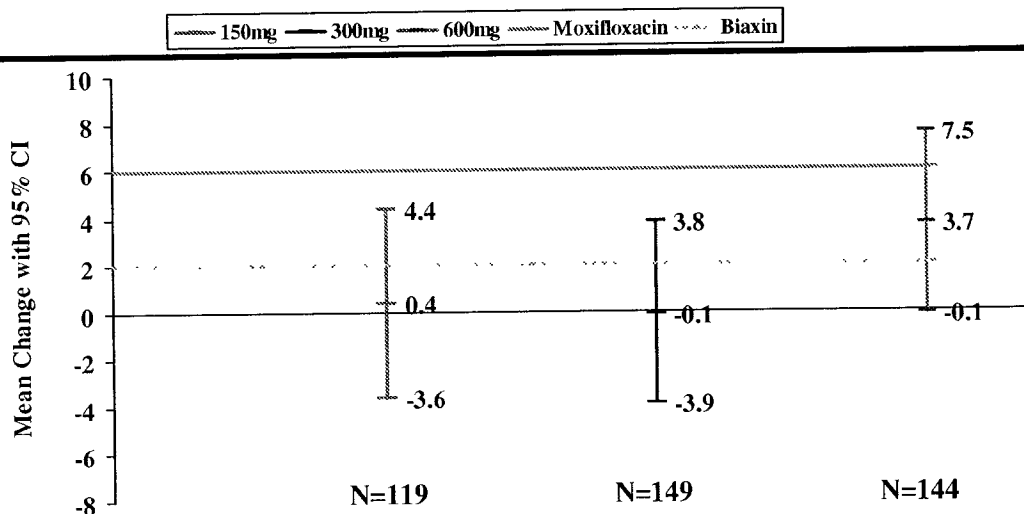
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- Total of 11 syncope reported
  - 5 were pre-dosing
  - 6 were post-dosing
- All associated with blood draw



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Mean Change of QTc from Pretreatment to During Treatment  
(Phase IIB - Based on Cardiologist Reading)



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***Phase IIA/B***

---

- 2 syncope reported
  - 1 was immediately upon first dose on Day 1 (600mg QD)
  - 1 was 7 days post last dose (100mg TID)



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***Liver Function***  
***Dave Morris***

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### *LFT Summary*

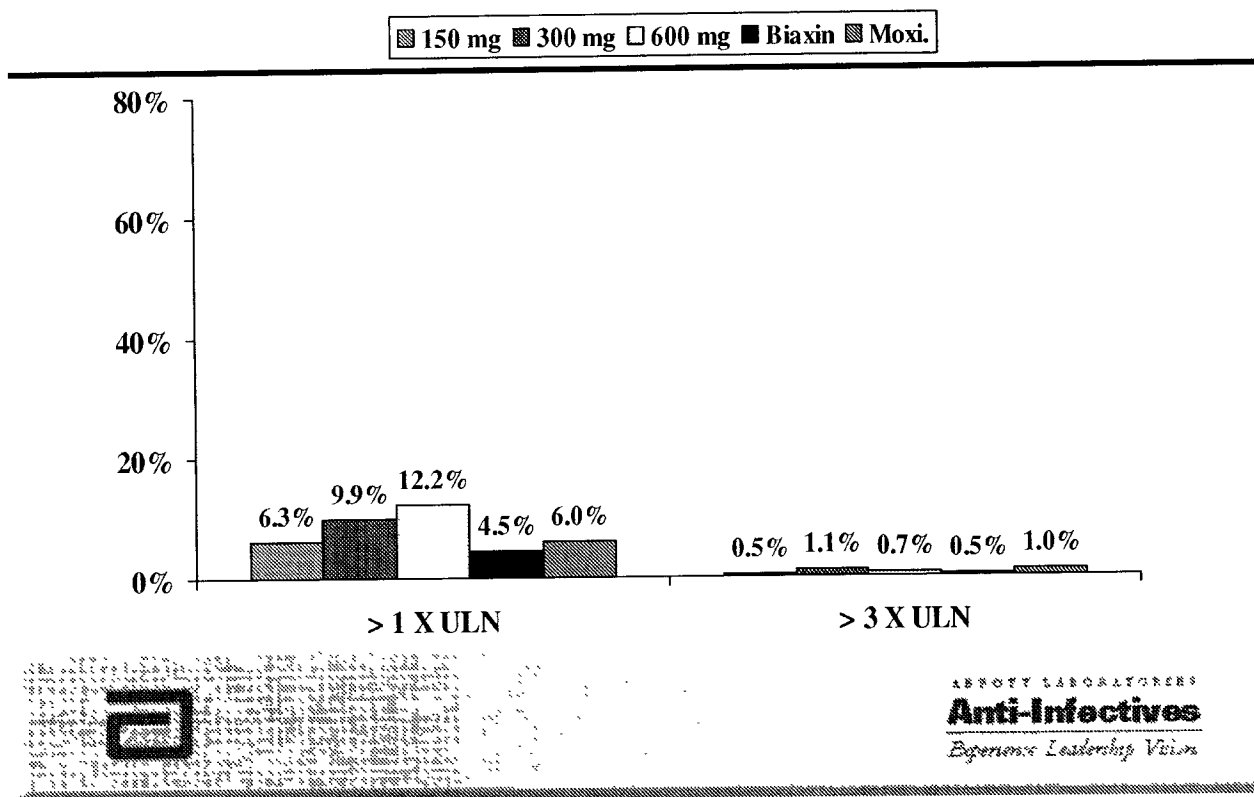
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- No evidence of LFT issue in Western subjects.
- No consistent evidence of dose response.
- Japanese bridging study results should be confirmed.
- Will continue to monitor LFT in Phase III programs.

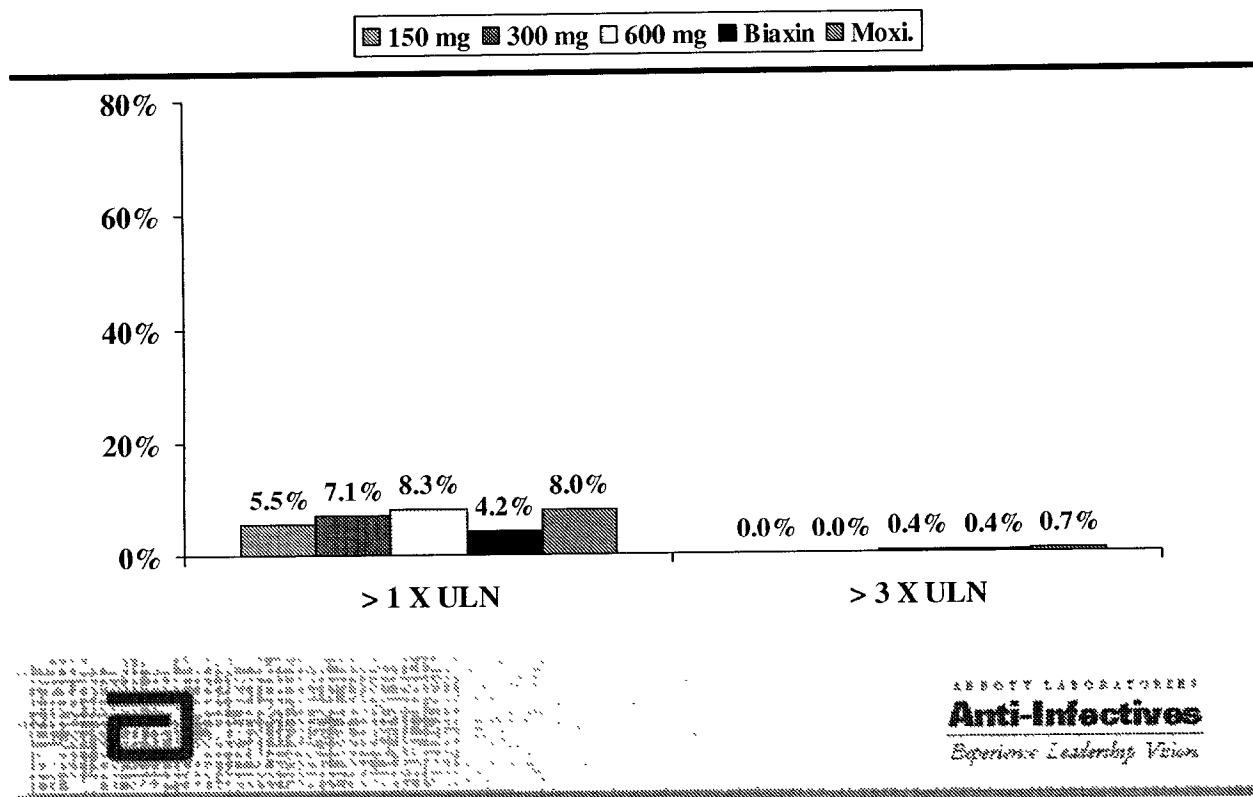


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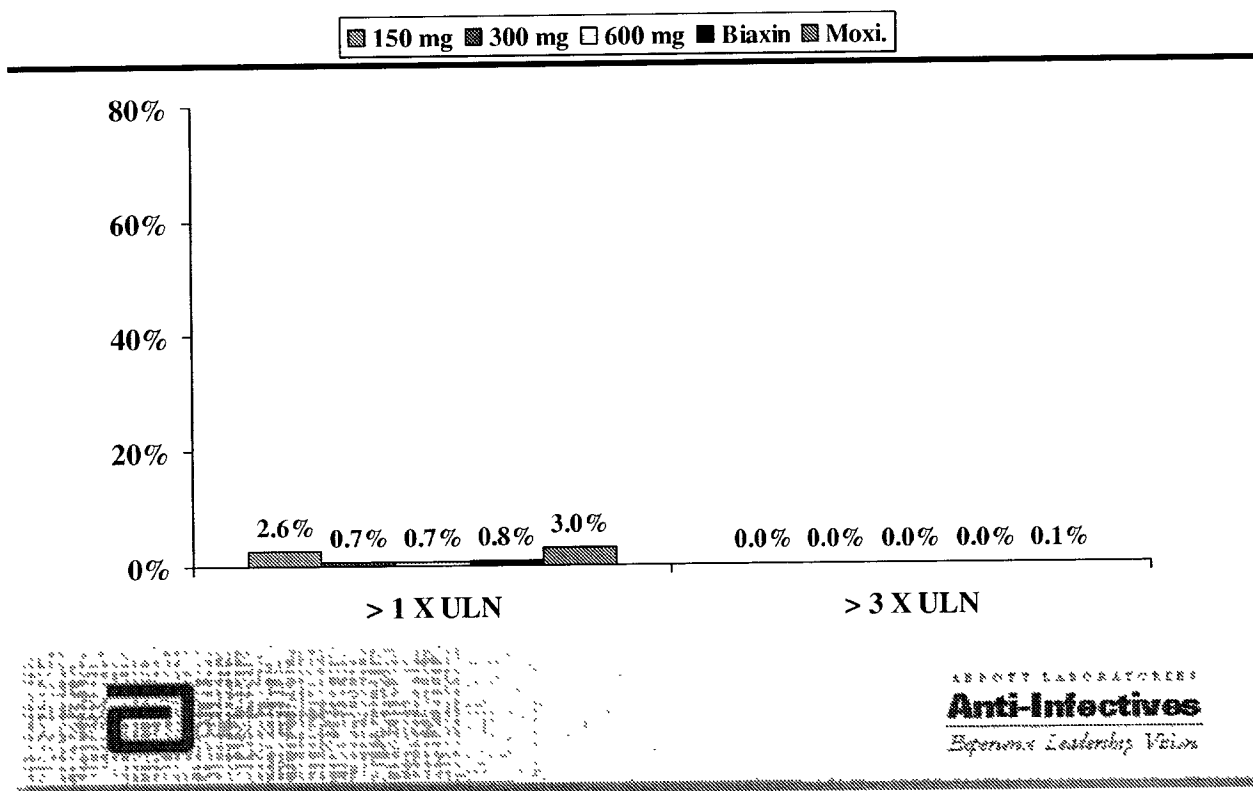
## Incidence Rate of SGPT Abnormalities



## Incidence Rate of SGOT Abnormalities



## Incidence Rate of Bilirubin Abnormalities



**Very high LFT Results: Phase II**

	SGPT*	SGOT*	GGT\$	Alkaline Phosphatase*	Total Bilirubin&
<b>150mg QD</b>					
% (N)	0/181	<1% (1/192)	<1% (1/183)	0/200	0/201
95% UL	2%3%	3%	2%	2%	
<b>300mg QD</b>					
% (N)	<1% (2/256)	<1% (1/267)	<1% (1/251)	0/278	0/288
95% UL	3%2%	2%	1%	1%	
<b>600mg QD</b>					
% (N)	<1% (1/256)	<1% (1/263)	0/252	0/273	0/287
95% UL	2%2%	2%	1%	1%	

\*: &gt;= 3\*NUL

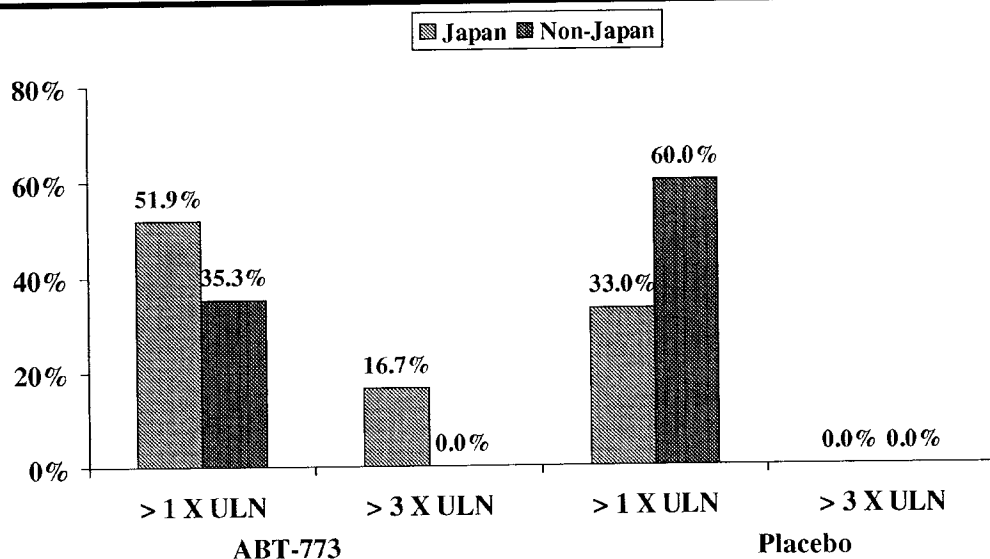
\$: &gt;=5\*NUL

&amp;&gt;=2 mg/dl.. Note: subject had normal LFT at baseline.



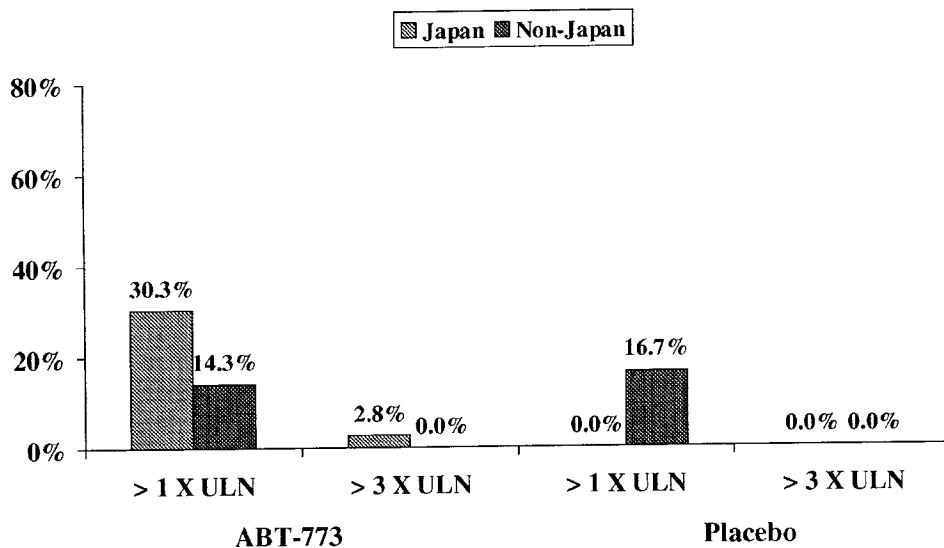
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## Incidence Rate of SGPT Abnormalities Japan Bridging Study



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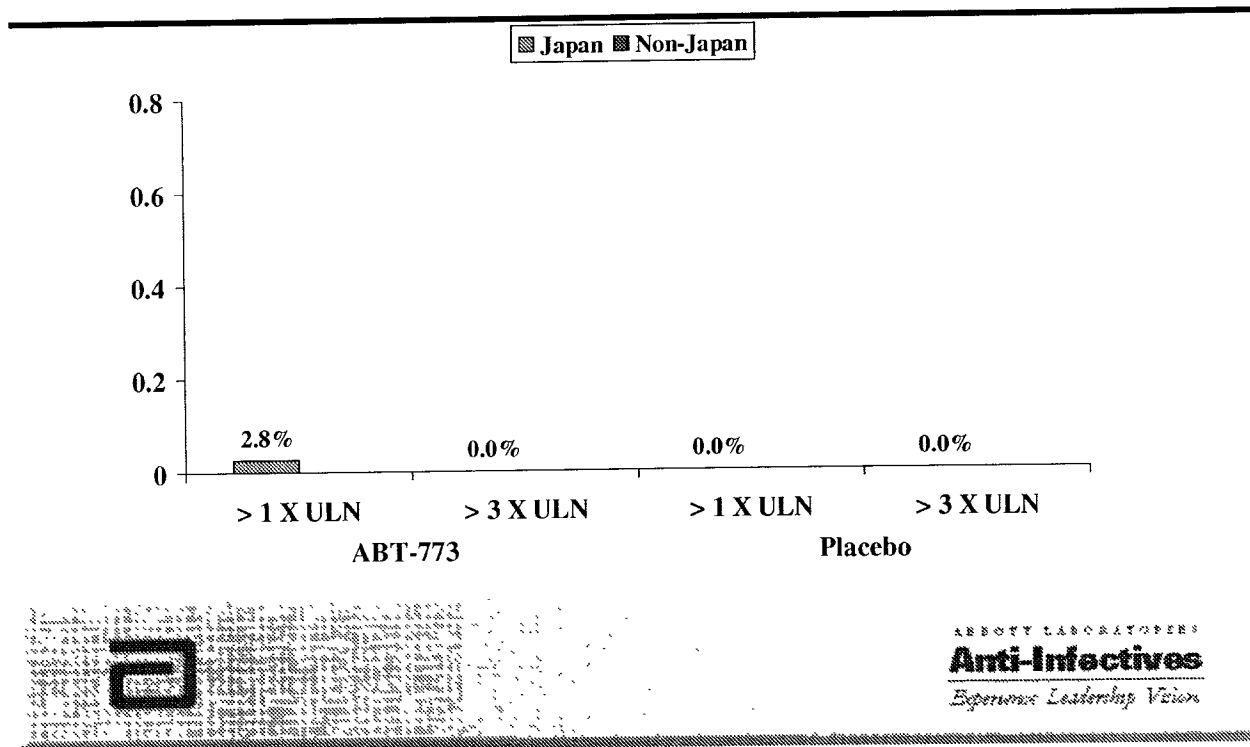
## Incidence Rate of SGOT Abnormalities Japan Bridging Study



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## Incidence Rate of Bilirubin Abnormalities Japan Bridging Study



***PK Profile***  
***Linda Gustavson***

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***Regulatory  
Jeanne Fox***

---



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ABBT205223

### ***ABT-773 Regulatory Status***

---

- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting 11/27/00
- End-of-Phase 2 CMC FDA meeting target 1/01
- Tablet NDA submission target 8/02



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### ***ABT-773 Regulatory Issues***

---

- **ABT-773 Potential for QT Prolongation**
  - QT issue is hot button for FDA
  - Question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QT
  - Required to include ECG monitoring in pivotal Phase 3 studies
- **ABT-773 Potential for QT Prolongation**
  - telithromycin (Ketek) data residing at FDA
    - Advisory Meeting scheduled for January
- **FDA may require a Phase 1 study in patients with underlying cardiac disease**
- **Some antimicrobials now contain warnings for QT prolongation**



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## ***ABT-773 Regulatory Issues***

---

- **ABT-773 Potential for Liver Toxicity**
  - Ketolides similar to macrolides?
  - Request for additional dog tox work
  - telithromycin (Ketek) data residing at FDA
    - Advisory meeting scheduled for January
- **Plan to conduct routine liver monitoring in all Phase 3 studies**



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### ***ABT-773 Regulatory Issues***

---

- Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of “macrolide-resistant *S. pneumo*”
- FDA will require “body of evidence”
  - excellent eradication of susceptible organisms
  - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients

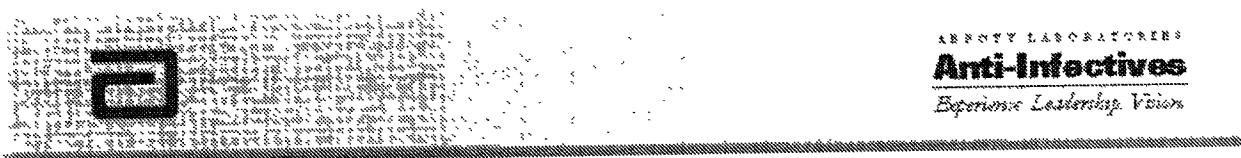


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## ABT-773 Regulatory Issues

- **Miscellaneous**

- Based on NDA timing, potential good candidate for E-submission
- Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
- Timing of pediatric program and "due diligence" for formulation development critical





***Commercial Profile, Positioning & Financials***  
***Rod Mittag***

---

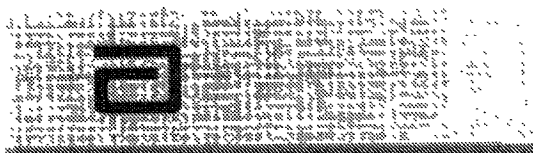


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***I.V. Program***  
***Carol Meyer***

---



ABBT205230  
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*Experience Leadership Vision*

**ABT-773 IV Program**  
*Formulation Objectives*

---

Reconstituted solution . Once a day dosing. Low pain on injection

Lyophilized powder, consisting of ABT-773 and a counterion base.

One strength, in a flip-top vial and the ADD Vantage system at launch.

Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.



## ***ABT-773 IV Formulation***

***Status***

---

- **PPD funded Program 01/00-08/00 (\$1.4MM)**
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- **HPD funded Program 08/00-12/00 (\$0.8MM)**
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program



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***ABT-773 IV Formulation***  
Animal Pain Study Results

---

- Assessed 6 prototypes( 3 different counterions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
- Results not conclusive
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.

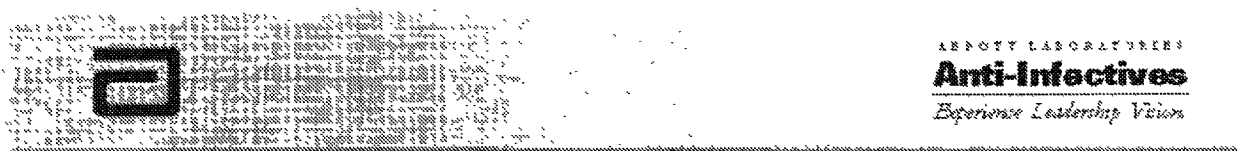


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*Beyond the Leadership Vision*

**ABT-773 IV**  
*Planned Clinical Program*

---

- |  |         |
|--|---------|
| • Single Dose -rising Phase I study        | Mar/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • Initiate Phase III                       | Oct/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |



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*Experience Leadership Vision*

**ABT 773 IV Program**  
*Summary*

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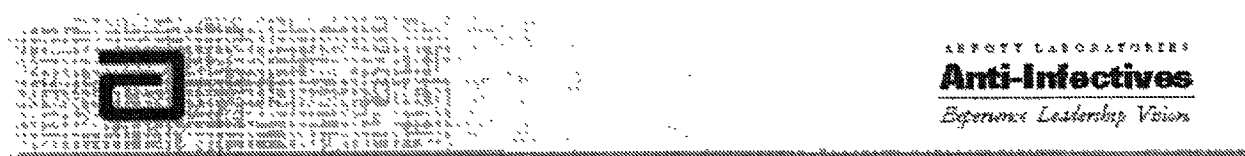
• **Comments**

- Funding for '01 not available with PPD/HPD
- Go/No go could be made after Phase I based on safety profile(pain,QT,GI)
- Milestone funding recommended (\$MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant S. pneumo claim



***Pediatric Program***  
*Carol Meyer*

---



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ABBT205236



***ABT-773 Pediatric Program***  
***Formulation Objectives***

---

- **Develop coated particle formulae for global use**

- Formulate coated particles for Suspension - 150mg/5mL & 300mg/5mL
- Formulate coated particles as a dry syrup, sprinkle or sachet.

- **Desired Properties**

- Once a Day Dosing
- Acceptable 'Initial Taste'
- Minimal 'After Taste'
- No Unpleasant Mouth-feel
- Acceptable Color and Flavor
- No Refrigeration Required.



### ***ABT-773 Pediatric Program***

***Status***

---

- Initiated January 2000
- 2000 Funding through first PK study milestone only (\$MM)
  
- Prototype Development completed (granules for suspension) May '00
- Phase I Single Dose Study - 2 prototypes completed Aug '00
- First set of Taste Evaluations completed Sep/00
- Comparative Taste vs Clari and Azi Dec/00



**ABT-773 Pediatric Program**  
*Formulation Trade-off*

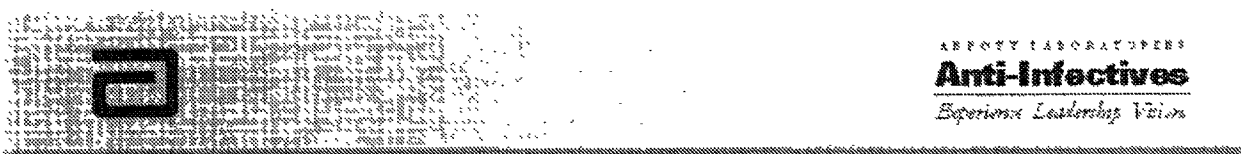
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ABT-773 Pediatric - Reconstitutable Suspension

Taste / Cost



Bioavailability



### ***ABT 773 Pediatric Program Challenges***

---

- **Pharmacokinetic Profile (plasma,middle ear fluid)**
- **Taste**
  - Masking Bitter Taste
  - Flavor
  - Mouth-Feel
- **Preserving the Reconstituted Suspension**
- **Ease of Manufacture**
- **Cost**



## ***ABT 773 Pediatric Program*** ***Formulation Development***

---

- **Formula Selected**

- Zein Coated Stearine 07 Based Particles
- Formula acceptable both from an Organoleptic and Dog Bioavailability standpoint
- Two prototypes
  - Same core
  - Different coating levels (15% and 25% coating)



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***ABT 773 Pediatric Program***  
Taste Assessment

---

- **Taste Assessment conducted by Arthur D Little**
  - Utilized a Flavor Profile Method of Sensory Analysis
- **Task 1: Sensory Analysis of Aqueous Solutions/ Suspensions of Uncoated Drug Substances**
  - ABT-773
  - Clarithromycin (Biaxin®)
  - Azithromycin (Zithromax®)
- **Task 2: Sensory Analysis of Coated ABT-773 Prototypes**



**ABT 773 Pediatric Program**  
Taste Assessment

**Sensory Analysis of Uncoated Drugs**  
*Summary of Results*

*The three drug substances can be ranked from most to least bitter as follows:*

<b>Drug Substance</b>	<b>Concentration (ppm) Which Exhibits an Initial Bitter Intensity <math>\leq 1</math> (Slight)</b>
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

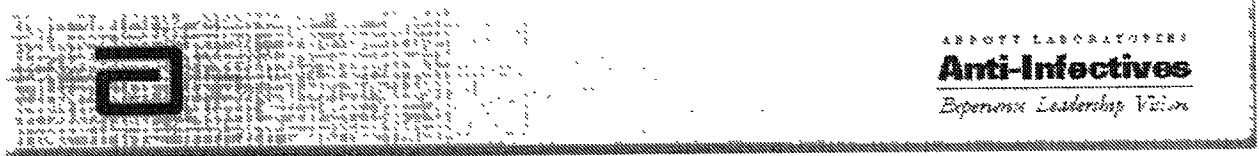
- ABT-773 is approximately five times more bitter than clarithromycin



***ABT 773 Pediatric Program***  
Taste Assessment

---

- **The flavor quality of the two coated drug prototypes was similar—the bitter intensity was moderate-to-strong initially and throughout the aftertaste.**
  - The observed bitter intensity is well above the “consumer concern level” of a slight intensity.
  - We believe that the lingering bitterness results from the “sustained release” of drug from the coated drug particles that lodge in the oral cavity (both prototypes exhibited a moderate amount of grittiness).



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**ABT 773 Pediatric Program**  
Phase I PK Results

- The AUC ratio (suspension:tablet) is 75% and the Cmax ratio is 77 to 79% for the two suspension formulations (SC-1a and SC-1b) respectively.

Pharmacokinetic Parameters	Tablet (N = 42)	Suspension (SC-1a) (N = 41)	Suspension (SC-1b) (N = 41)
T <sub>max</sub> (h)	3.0 ± 1.3	2.6 ± 1.0	2.8 ± 1.0
C <sub>max</sub> (ng/mL)	628 ± 263	505 ± 234	494 ± 223
AUC <sub>∞</sub> (ng•h/mL)	4527 ± 1830	3645 ± 2226	3521 ± 1868
t <sub>1/2</sub> (h)‡	6.3	6.8	6.7
C <sub>max</sub> Ratio (test/ref)*	---	0.79	0.77
AUC <sub>∞</sub> Ratio (test/ref)*	---	0.75	0.75

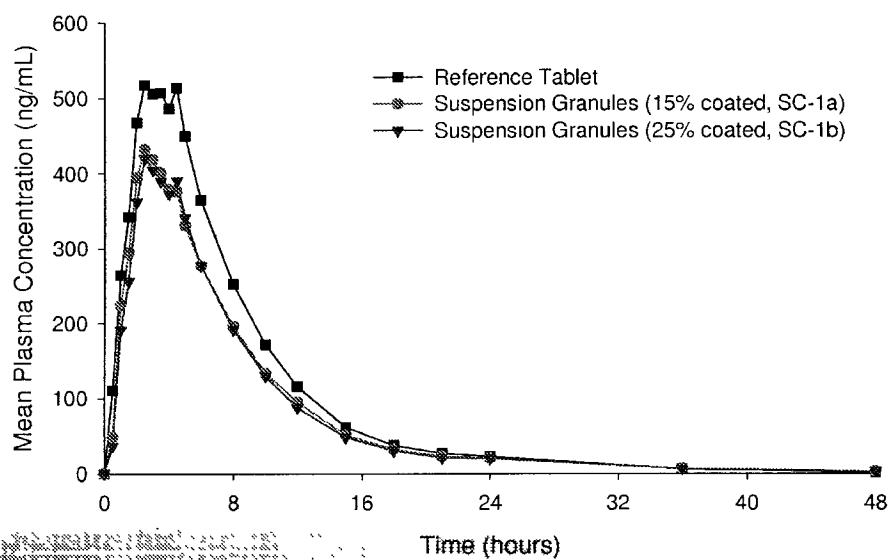
‡ Harmonic mean

\* Geometric mean



**ABT 773 Pediatric Program**  
Phase I PK Results

**Study M00-196: Preliminary Mean ABT-773 Plasma Concentration-Time Profiles**



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**ABT 773 Pediatric Program**  
Proposed Clinical Program

Proposed Pediatric Clinical Studies for Registration (Phase 1, 2, 3)			
Indications/Type	Phase	No. of Studies	No. of Subjects
PK adult single rising dose, multiple rising dose/effect of food	1a 1b	4	96
Otitis Media (dose ranging), PK in children	2	1	100
Otitis Media, Pharyngitis, CAP	3	6	1800



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***ABT 773 Pediatric Program***  
Proposed Clinical Program

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- **First option**
  - Develop a pro-drug with no immediate after taste , stable in a suspension formulation , hydrolized in acidic pH and absorbed as parent drug.
  - Three pro-drugs under study (benzoyl,TMB,ES)
- **Second option**
  - Continue improving after taste,PK of parent drug formulation.
- **Recommend first option with Go/No go in 06/01 (\$MM)**



***Japan Program***  
*Carol Meyer*

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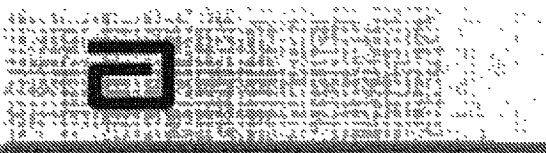
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***Japan Program***  
*Taisho*

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- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan
- Findings in first PK trial in Hawaii resulted in repeat of Phase I in Japan



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## ***Japan Program*** ***Phase I Findings***

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- Initial Phase I study conducted in Hawaii with Japanese and non-Japanese subjects
- Results indicate 50% higher AUC and Cmax in Japanese vs non-Japanese
- Liver enzyme elevations were noted in a few Japanese subjects, however it was not dose related
- Decision made to repeat Phase I in Japan



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**Japan Program**  
*Clinical Plan*

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• **Phase I in Japan**

- |   | <u><b>Start</b></u> |
|---|---------------------|
| – Food Effect Study                                   | Nov/00              |
| – Single and multiple dose study                      | Dec/00              |
| – Review data (Abbott/Taisho)                         | April/01            |
| • PK data Japanese vs Caucasian                       |                     |
| • Development program strategy                        |                     |
| – Present Kiko data and recommend development program | May/01              |
| – Start Tissue Conc. Study                            | 2Q/01               |

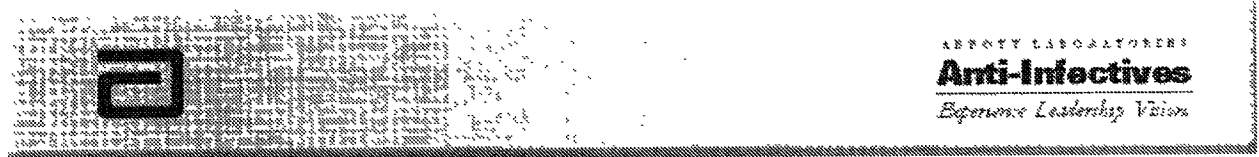




***Japan Program***  
***Clinical Plan***

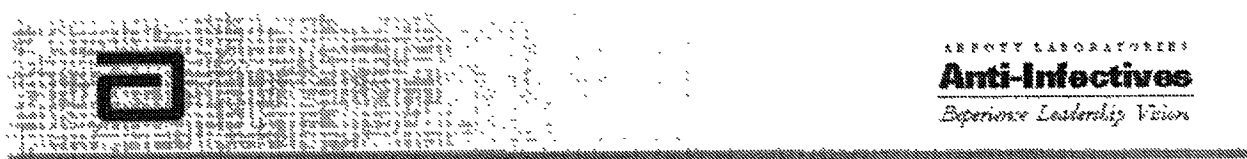
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- **PK similar in Japanese and Caucasians (12/02 filing)**
- **Recommend to Kiko same dose in Japan as in ex-Japan**
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in SSS, Dentistry, Otolaryngology, UTI and pan- bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- **PK different in Japanese and Caucasians(12/03 filing)**
  - Phase II dose ranging study in CAP (Bridging study)
  - -Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing



**Summary**  
*Carl Craft*

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***Backups***

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**Competitive Update, Ketek-Rod Mittag**  
**OS/IV/overall financials-Rod Mittag**



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***IV/OS/Overall Financials***

**Rod Mittag**



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